FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEES

(AADPAC and DSaRM)

Open Session

Wednesday, June 8, 2016

9:29 a.m. to 3:55 p.m.

FDA White Oak Campus

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

P R O C E E D I N G S

(9:29 a.m.)

Call to Order

Introduction of Committee

DR. BROWN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so.

I'd also like to identify the FDA press contact who is Michael Felberbaum who is waving in the back.

My name is Rae Brown. I'm the acting chairman for today's meeting. I will now call the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introduce ourselves. We'll start with the FDA to my left and go around the table.

DR. STAFFA: Good morning. My name is Judy Staffa. I'm the acting associate director for public health initiatives in the Office of

Surveillance and Epidemiology in CDER.

DR. HERTZ: Sharon Hertz, director, Division of Anesthesia, Analgesia, and Addiction Products in CDER.

DR. FIELDS: Ellen Fields, deputy director in the same division.

DR. GUPTA: Dr. Anita Gupta, I'm vice chair of anesthesiology. I'm a pharmacist at Drexel University College of Medicine in Philadelphia.

DR. BESCO: Good morning. My name is Kelly Besco. I'm a pharmacist and health systems medication safety officer for the Ohio Health Hospital System in Columbus, Ohio.

DR. WINTERSTEIN: Good morning. I'm Almut Winterstein. I'm professor and chair for pharmaceutical outcomes and policy at the University of Florida.

DR. MORRATO: Good morning. This is Elaine Morrato. I'm in the Department of Health Systems Management and Policy and associate dean for public health practice at the Colorado School of Public Health, University of Colorado.

DR. SHOBEN: I'm Abby Shoben. I'm an assistant professor of biostatistics at the Ohio State University.

DR. BEGANSKY: Stephanie Begansky. I'm the designated federal officer for today's meeting.

DR. BROWN: Rae Brown. I'm a pediatric anesthesiologist and professor of anesthesiology and pediatrics at the University of Kentucky.

DR. KAYE: Alan Kaye. I'm a professor, program director, and chairman of anesthesia at LSU School of Medicine in New Orleans.

DR. EMALA: Charles Emala. I'm professor of anesthesiology, vice chair for research, Columbia University, New York.

DR. McCANN: Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's Hospital and associate professor at Harvard Medical School.

DR. CAMPOPIANO: Melinda Campopiano. I'm a family physician and addiction medication specialist, and I'm a medical officer and branch chief for regulatory programs in the division of

pharmacologic therapies at the Substance Abuse and Mental Health Services Administration.

DR. SPRINTZ: Hi, Michael Sprintz. I'm an anesthesiologist, pain medicine specialist and addiction medicine specialist, chief medical officer of the Sprintz Center for Pain and Dependency.

DR. PERRONE: Jeanmarie Perrone. I'm an emergency physician, and the director of medical toxicology, and a professor of emergency medicine at the University of Pennsylvania School of Medicine.

DR. HIGGINS: Jennifer Higgins, consumer representative.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist and associate professor of pharmacy at Rutgers University.

DR. HERRING: Hi. Joe Herring. I'm a clinical neurologist employed at Merck in the clinical nerve science group and the industry representative.

DR. BROWN: Welcome to the committee. For

topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please

refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Lieutenant Commander Stephanie Begansky, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. BEGANSKY: Thank you.

Good morning, everyone. The Food and Drug Administration is convening today's joint meeting of the Anesthetic and Analgesic Drug Products advisory committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of these committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflict of interest laws covered by but not

limited to those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as

well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, writing, speaking, patents and royalties, and primary employment.

Today's agenda involves the discussion of new drug application 207621, oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules submitted by Pfizer with the proposed indication of management of pain severe enough to require daily around-the-clock long-term opioid treatment and for which alternative treatment options are inadequate.

The product is an extended-release formulation intended to have abuse-deterrent properties based on the presence of naltrexone, an opioid antagonist, in the formulation. The committees will be asked to discuss whether the data submitted by the applicant are sufficient to support labeling of the product with the properties

expected to deter abuse.

This is a particular matters meeting during which specific matters relating to Pfizer's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Joseph Herring is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Herring's role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck.

We would like to remind members and temporary voting members that if the discussions

involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. BROWN: We will now proceed with the FDA's introductory remarks from Dr. Ellen Fields.

FDA Introductory Remarks - Ellen Fields

DR. FIELDS: Good morning, Dr. Brown, members of the Anesthesia and Analgesia Drugs Advisory Committee, members of the Drug Safety and Risk Management Advisory Committee, and invited guests. Thank you for joining us today.

For many of you, this is your second day with us, and we sincerely thank all of you for spending your valuable time at this meeting. To those who were here yesterday, my comments may

sound very familiar, but today, we're here to discuss an application from Pfizer for a new extended-release capsule formulation of oxycodone hydrochloride and naltrexone with the proposed trade name Troxyca ER.

If approved, Troxyca ER will have the same indication as the already approved extended-release long-acting opioid analgesics, that is, the management of pain severe enough to require daily around-the-clock long-term opioid treatment and for which alternative treatment options are inadequate.

Troxyca ER has been formulated with naltrexone, an opioid antagonist, sequestered within small pellets that are coated with oxycodone. The presence of naltrexone is intended to provide abuse-deterrent properties when the product is manipulated.

With oral administration of intact capsules or pellets sprinkled on applesauce, the intention is there is little or no exposure to naltrexone. However, physical and/or chemical manipulation of the pellets is intended to release naltrexone,

which will antagonize the effects of oxycodone and block its reinforcing effect by the oral intranasal and intravenous routes of administration.

During this meeting, you will hear presentations from Pfizer on the development program for Troxyca ER, the in vitro physical and chemical manipulation studies and the human abuse potential studies they conducted to demonstrate abuse-deterrent properties.

FDA will present drug utilization for oxycodone and other extended-release opioids as well as the proposed labeling regarding the in vitro and in vivo abuse-deterrent studies that were conducted by the applicant.

We are aware of the immense public health problem that exists in the United States today from the abuse of prescription opioids. As part of a larger effort across HHS, we at FDA have encouraged drug companies to develop novel intervention to reduce or, when possible, prevent abuse.

To this end, we have supported the development of novel formulations through multiple

interactions with both the pharmaceutical industry and academic community. And in April 2015, we issued the guidance for industry, abuse-deterrent opioids, which explains the agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. It makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

In response to the growing epidemic of opioid abuse, dependence, and overdose in the United States, the commissioner announced an opioid action plan in February of this year to take steps toward reducing the impact of opioid abuse on public health.

As part of this plan, the agency has committed to work more closely with its advisory committees before making critical product and labeling decisions. And as you know, we are calling on all of you more often to fulfill this goal.

As we work to make opioid analgesics less desirable targets for abuse, we cannot forget that the underlying purpose of these products is the management of pain in patients for which other alternatives are inadequate. And opioid analgesics remain an important component of pain management.

The greater amount of opioid available in many extended-release opioid analgesics relative to immediate-release products is associated with greater risk for overdose and death, but also makes these a desirable target for those seeking to abuse opioids. However, immediate-release opioids are also abused, and the development of abuse-deterrent immediate-release formulations that can reduce abuse is also an important public health goal.

While the most common route of abuse for opioids is oral, the risk for infection and overdose associated with intravenous and nasal routes makes these routes of abuse important targets for abuse-deterrent properties.

With every new product, we weigh the risk and benefits. With new abuse-deterrent

formulations, we are also watchful for any evidence that the product results in a new or increased safety risk for patients who take the product as directed as discussed in an advisory committee last September, and for any evidence that by deterring abuse by one route of administration, the new product may shift abuse to a riskier route of administration; for example, by deterring oral abuse but inadvertently making nasal or intravenous abuse more attractive.

There are currently six approved extended-release opioid products with abuse-deterrent properties, and we are watching the postmarketing data closely for any signs of unintended problems associated with these products.

Today, you will be asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling the routes of abuse for which abuse-deterrent properties have been demonstrated, and whether Troxyca ER should be approved.

These are clearly difficult questions for

which there are no easy answers. We are asking that you provide your expertise, your experience, and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us and look forward to this important discussion.

Now I just want to introduce Dr. Ben Stevens, who will go over some corrections that we'd like to make to the agency's open session backgrounder. There's a copy of the slides that have been placed in the packet of slides for today, and he will go over it. It will just take a couple of minutes.

Presentation - Benjamin Stevens

DR. STEVENS: Good morning. So as Ellen noted, I'm just going to go through a couple of corrections that we're making to the FDA's section of the open session backgrounder related to the in vitro abuse-deterrent studies and results that

we presented in the document.

So I'll just go through line by line, starting with the top left-hand corner for the open session backgrounder, page 52 in the errata. The text from the FDA states, section 1(b), first paragraph, second sentence, "The formulation was defeated in the following solvents when extracted for 12 hours or longer using intact pellets; common solvents, A, G, K, and N."

Solvent K should be removed, so it should just be A, G and N, and I should mention at this point in time that the vast majority of these corrections are associated with errors in the coding scheme that we used.

For the second line, open session backgrounder, page 52 in the errata, section 1(b), first paragraph, third sentence, "When common solvent K was used, 90 percent of the oxycodone was extracted in three hours or more," this should be six hours or more.

Page 53 in the errata, section 1(b), second paragraph, "When crushed pellets were used for

extraction study, no oxycodone could be extracted in common solvents A and G." This sentence should be removed.

For the open session backgrounder page 53, section 1(b), second paragraph, "When common solvents I were used, about 40 to 50 percent of oxycodone in 30 minutes or less was isolated," this should be solvent O instead of solvent I.

On to the second slide, open session backgrounder, page 52, text under section 1(b), second paragraph, "Under stress conditions, 80 to 90 percent of the oxycodone was isolated within one to four hours of extraction time using intact pellets. With crushed pellets, no oxycodone was isolated." This last sentence in this section, "With crushed pellets, no oxycodone was isolated," should be deleted.

Open session backgrounder, page 53, section 1(b), paragraph 4, "Common solvents L to N are particularly effective at extracting oxycodone from intact pellets." This should be changed from L to N into K to M.

Finally, open session backgrounder errata in the conclusion in the backgrounder page 54, part 1(d), second paragraph, "Common solvents B to E appear to be capable of removing naltrexone selectively from crushed ALO-02." This sentence should be deleted, so the entire sentence should be removed.

So at this point in time, I'll turn it over to the applicant for their presentation.

DR. BROWN: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's nonemployee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria or interest in a sponsor, including

equity interest and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

Applicant Presentation - Sean Donevan

DR. DONEVAN: Good morning. My name is Sean Donevan, and I'm the medical affairs lead for the opioid program at Pfizer. I'm pleased to be here today to present ALO-02 to the advisory committee, to the FDA and to the public. And just for the sake of clarity, we'll be referring to Troxyca as ALO-02 in this presentation. I just wanted to make that clear. Thank you.

It is well recognized that opioids are a powerful pain medication and for some patients are an essential component of their treatment approach. However, opioids are also associated with serious

public health problems such as abuse, addiction, and deaths from opioid overdose.

Abuse-deterrent opioids are an important part of a multifaceted, multi-stakeholder approach to address opioid abuse. The objective of abuse-deterrent opioids is to provide pain relief for patients when an opioid is necessary but also to reduce the consequences associated with abuse or misuse.

The objective of today's meeting is to determine if our abuse-deterrent program for ALO-02 supports its labeling as an abuse-deterrent opioid.

ALO-02 is a pellet in capsule formulation. Each pellet consists of a core of sequestered naltrexone that is surrounded by a layer of extended-release oxycodone. Naltrexone is an antagonist of opioid receptors and will block the effects of opioid agonists such as oxycodone, and the ratio of naltrexone to oxycodone in the pellets is 12 percent by weight. The different dosage strengths are developed by increasing the amount of these common pellets in each capsule.

When the product is taken as directed and swallowed intact, the naltrexone is intended to remain sequestered, and the patient only experiences the intended effects of the release of oxycodone. When the product is crushed or manipulated as an abuser might do, then naltrexone is released and would antagonize the effects of oxycodone.

This is the same naltrexone technology that is in Pfizer's Embeda. Embeda contains extended-release morphine and sequestered naltrexone, and it received abuse-deterrent labeling in October of 2014.

It's important to highlight that with this technology, there are no visual cues to the abuser that they have defeated the formulation. The only way abusers can determine if they have defeated the formulation is to try it on themselves.

An analysis of abuser comments about Embeda on chatroom internet sites indicate that these abusers are fearful of withdrawal from the naltrexone in Embeda, and this fear alone deters

some from experimenting from Embeda. We would expect a similar barrier to experimentation with ALO-02.

This outlines the agenda for Pfizer's presentation this morning. I will first provide a brief introduction and then turn the podium over to my colleagues who will present key findings from the ALO-02 development program with an emphasis on our abuse-deterrent program.

In addition to the Pfizer presenters, I'd also like to acknowledge the experts who are attending the advisory committee on Pfizer's behalf. This includes Dr. Edward Cone, Dr. Richard Rauck, Dr. Richard Dart and Dr. Edward Sellers. Their affiliations and areas of expertise are listed on this slide.

The NDA for ALO-02 was submitted to the FDA in December of 2014 as a 505(b)(2) application. We referenced Roxicodone for the safety and efficacy of oxycodone in ALO-02 and Revia for the safety of naltrexone.

In today's presentation, we will show you

that the Category 1 data from our in vitro laboratory manipulation and extraction studies and the Category 2 and Category 3 data from our clinical abuse potential studies supports abuse-deterrent labeling. Likewise, we will show that our phase 3 program confirmed the safety and efficacy of ALO-02 in chronic pain patients.

In their guidance, the FDA identified seven major categories of abuse-deterrent opioids. The majority of currently available abuse-deterrent opioids are physical chemical barrier approaches which are difficult to manipulate, resist extraction of the opioid, and often form viscous gels when added to aqueous solvents.

ALO-02 is an example of an agonist/antagonist combination approach, and this is the first abuse-deterrent ER oxycodone to use a sequestered naltrexone technology. Other currently available extended-release oxycodone abuse-deterrent opioids use a physical chemical barrier approach.

I show this slide to indicate the various

routes of abuse that opioid abusers will use to get their high. The predominant route of abuse is the oral route of abuse, especially for immediate-release opioids in which the abuser will either swallow multiple pills intact or crush or chew the tablet and then swallow either alone or together with water or alcohol.

On the other hand, there are other non-oral routes of abuse. Non-oral routes of abuse can be quite common with extended-release opioids. Furthermore, abusers will often start by abusing by the oral route and then switch to non-oral routes of administration.

Not only are these non-oral routes of administration common with ER opioids, but these routes of abuse are also more dangerous. Studies have shown that the relative risk of serious health consequences, including death, are higher with non-oral routes of abuse compared to oral routes of abuse.

Abusers will often crush and then snort the crushed powder. Alternatively, an abuser might

take the crushed or intact tablet or capsule, add it to small volumes of water, heat the solution, and then withdraw the liquid into a syringe, and inject intravenously.

Finally, a fourth route of abuse is smoking. This route of abuse is relatively infrequent with extended-release opioids, but it does occur.

To understand the ability of an abuse-deterrent opioid to deter abuse by these different routes of administration, the FDA in their guidance has provided a testing approach that includes a combination of in vitro laboratory-based studies and clinical studies in recreational opioid abusers. This guidance is outlined in the next slide.

The FDA guidance identified four categories of studies that can be done to investigate the abuse-deterrent properties of an abuse-deterrent opioid. Three of these categories can be done prior to approval, and these can support abuse-deterrent labeling while Category 4 studies can only be initiated after the approval and launch of

the drug.

Category 1 studies are the in vitro laboratory manipulation and extraction studies. Category 2 studies evaluate the pharmacokinetic properties of the manipulated formulation, and Category 3 studies evaluate the abuse potential of the compound in recreational drug abusers.

For opioids with abuse-deterrent labels, the results of these Category 1, 2, and 3 studies are described within section 9.2 of the label along with a summary of the expected reductions in abuse by the different routes of administration.

This slide describes the development program for ALO-02. The development program included clinical pharmacology studies to describe the bioequivalence of ALO-02 to oxycodone and other important pharmacokinetic properties of ALO-02.

The phase 3 program demonstrated the efficacy and safety of ALO-02 in chronic pain and consisted of two studies. Study 1002 was a 12-week efficacy study in chronic low back pain while study 1001 was a long-term open-label study in chronic

non-cancer pain patients that assessed the safety as well as the effectiveness of ALO-02 with up to 12 months of treatment.

Finally, and the reason why we're here today, is our abuse-deterrent program. This program consisted of in vitro laboratory studies as well as three abuse potential studies that demonstrated simultaneous release of oxycodone and naltrexone with crushed ALO-02 administration. They also demonstrated a reduction in abuse potential by the oral and intranasal route as well as the intravenous route with crushed ALO-02 in recreational drug abusers.

With that as a general introduction, we will now discuss the development program for ALO-02, and with that, I will turn to podium over to Dr. Malhotra, who will discuss the key findings from the clinical pharmacology program.

Applicant Presentation - Bimal Malhotra

DR. MALHOTRA: Thank you, Dr. Donevan.

It is important to assure that ALO-02 can deliver therapeutic amounts of oxycodone equivalent

to its immediate-release reference formulation at the same dose while keeping naltrexone sequestered. To demonstrate this, a relative bioavailability study compared 40 milligrams of ALO-02, in blue diamonds, with 20-milligram oxycodone in IR reference, in orange squares.

Subjects were dosed without naltrexone block, hence 20-milligram Roxicodone was given. The results of this study showed that oxycodone bioavailability from ALO-02 was equivalent to Roxicodone as assessed by dose normalized AUC ratios falling within 80 to 125 percent.

Oxycodone half-life was approximately seven hours, which was prolonged, which assures that ALO-02 can be given twice daily.

Of importance, naltrexone concentrations were not detectable in any samples after ALO-02 dosing. That is, they were below the quantitation limit of 4 picograms per mL.

Now let's focus on the unique extended-release profile of ALO-02, in particular, parameters that are correlates of abuse potential.

Tmax for ALO-02 was delayed to 12 hours compared with one hour for oxycodone, and Cmax for ALO-02 was markedly reduced to 33 percent of that for oxycodone.

This very slow and delayed absorption of oxycodone from intact ALO-02 is likely to result in less drug liking even when the formulation is not manipulated but intact.

In the food effect study, 40-milligram doses of ALO-02 without a naltrexone block were given as capsules with a high-fat meal, shown in blue squares, or in the fasted state, shown in yellow circles, and also as pellets sprinkled in applesauce, shown in green triangles. For each treatment, the PK profiles of oxycodone were nearly superimposable.

Cmax and AUC values included bioequivalence between fed and fasted and sprinkled in applesauce versus fasted treatments. Naltrexone concentrations are not shown on this profile, but were undetectable in all of the samples in each treatment.

Thus, ALO-02 can be taken without regards to meals. For patients who have difficulty swallowing intact capsules, the pellets may be sprinkled on applesauce and taken without chewing.

Another study was conducted to assess ethanol interaction with ALO-02 20-milligram doses under a naltrexone block. In this study, ALO-02 was given with 20 percent ethanol, shown in green squares, with 40 percent ethanol shown in purple triangles, or with water, shown in blue circles.

As you can see, there is no effect of taking ALO-02 with 20 percent ethanol on oxycodone PK. The 90 percent confidence intervals for Cmax and AUC ratios were within 80 to 125 percent.

When it was taken with 40 percent ethanol, there was a 37 percent increase in Cmax and 13 percent increase in AUC. This increase was not considered to be an overexposure to oxycodone, especially when you compare to exposures following the same dose of an IR formulation, which I've shown in orange diamonds from a different study.

Based on the delayed Tmax and considerably

lower Cmax, ALO-02 taken with 40 percent ethanol is still maintaining an extended-release profile of oxycodone. Furthermore, there is no indication of dose dumping when ALO-02 is taken with either 20 or 40 percent ethanol.

Now I'd like to invite Dr. Gernot Wolfram to the podium to share the efficacy and safety results.

Applicant Presentation - Gernot Wolfram

DR. WOLFRAM: Good morning. The clinical program for ALO-02 included the efficacy study 1002 and the 12-month safety study 1001. Here, you can see the design of the efficacy study 1002.

Patients with chronic low back pain of at least three months, pain score of 5 or more and who needed a continuous around-the-clock analgesic for an extended period of time were converted and titrated to effect with doses between 10 to 80 milligrams of ALO-02 twice daily. Up to 3 grams acetaminophen per day were allowed as rescue medication.

Of 663 screened patients, 410 entered the

open-label titration phase, where all subjects received active ALO-02 treatment. At the end of the open-label titration phase, patients tolerating ALO-02 with pain scores of 4 or lower were then randomized to either continue on active ALO-02 or placebo treatment.

To protect the integrity of the placebo-controlled group, patients were tapered off treatment over two weeks in a blinded manner starting at randomization.

One hundred thirty-four patients were randomized into the placebo group and 147 patients into the ALO-02 treatment group. After 12 weeks, patients were tapered off study treatment during a two-week follow-up period, at which doses in the active form of the double-blind phase were 65 milligrams per day of ALO-02.

A significant reduction of pain over 12 weeks was observed at the primary study endpoint. Baseline pain scores of around 7 at screening decreased to around 3 points at the end of the titration period. From the time of randomization

until the end of the 12-week control period of the study, pain scores were 4.3 and 3.6 for placebo and ALO-02, respectively. The treatment difference between both groups, as you can see, was statistically significant, establishing efficacy of ALO-02.

The observed adverse events were consistent with known opioid side effects. Here, you can see the adverse event profile for ALO-02 during the 12-week study with the AEs ordered according to the incidence of occurrence during the open-label titration phase.

Sixty-three percent of subjects experienced an adverse event during the open-label titration phase and 56 or 57 percent during the double-blind phase for placebo or ALO-02. Nausea, constipation and vomiting were the leading AEs, which is the typical profile for opioids.

Study 1001 was a 12-month multicenter, open-label, single-arm safety study to establish the safety for ALO-02. The study was conducted in patients with chronic non-cancer pain of at least

three months' duration and a pain score of 5 or more.

Again, patients needed to be on a continuous around-the-clock opioid analgesic for an extended period of time. Patients are then converted and titrated to affect these doses between 10 and 80 milligram ALO-02 twice daily and up to 2 grams of acetaminophen per day were allowed as rescue medication.

Three hundred and ninety-five patients qualified for inclusion into the study. Patients were titrated to effect and treatment with ALO-02, adjusted based on inadequate analgesia, defined as pain of greater than 4.

At the end of the 12-month open-label phase, patients were tapered off during a two-week post-treatment period, at which doses during the maintenance phase were around 63 milligrams per day of ALO-02.

A significant reduction of pain was observed over a prolonged time of 12 months. Baseline scores for average pain in yellow triangles at

screening of around 6 points decreased to around 4 points about four weeks into the treatment. A similar pattern was observed for worst pain scores, as seen in red squares.

This level of pain reduction was maintained over the entire 12-month period of the study, and changes in pain scores from baseline were statistically significant at all visits.

Again, the observed adverse events were consistent with known opioid side effects. You can see the adverse event profile for ALO-02 during the 12-month study with AEs ordered according to the incidence of occurrence. Sixty-six percent of subjects experienced an adverse event, and again, nausea, constipation and vomiting were the leading AEs which is again a typical profile for opioids.

Thank you, and I'm handing back to Sean Donevan, who will lead you through the in vitro part of the abuse-deterrent program.

Dr. Donevan.

Applicant Presentation - Sean Donevan

DR. DONEVAN: Thank you, Dr. Wolfram.

As I described earlier and outlined in this slide, our development program for ALO-02 also included a comprehensive package of studies to evaluate the abuse-deterrent features of ALO-02. I will discuss data from our Category 1 in vitro manipulation and extraction studies, and then Dr. Roland will describe the Category 2 and Category 3 from the oral, intranasal and intravenous human abuse potential studies that were conducted in recreational drug users.

The design of the in vitro program for ALO-02 was developed based on an understanding of the formulation, and the program is different from what one would do from a typical physical chemical barrier abuse-deterrent opioid.

Naltrexone is intended to be released from ALO-02 with crushing to counteract the effects of oxycodone. Thus extensive crushing and manipulation studies that are characteristic of the physical chemical barrier platforms are not relevant to ALO-02.

To address the IV routes of abuse, we

examined extraction of oxycodone and naltrexone is small-volume extraction studies. Because the formulation does not contain excipients that form a viscous gel, we did not assess syringeability and injectability.

The abuse-deterrent features of ALO-02 rely on the slow extended release of oxycodone when ALO-02 is taken intact and the release of naltrexone together with the oxycodone when ALO-02 is crushed.

The key objective of the in vitro program was to explore the ability to defeat or compromise the formulation. We sought to identify those conditions that would disrupt the extended-release properties of ALO-02 and allow for the rapid and selective extraction of oxycodone in the absence of naltrexone from either crushed or intact ALO-02.

We found that with crushed ALO-02 pellets, naltrexone was released together with oxycodone in 30 of 31 solvents. We did identify some conditions in solvents with intact pellets that resulted in the disruption of the extended-release properties

of the formulation. However, in most conditions and most solvents, there was only a brief window of time before there was significant extraction of naltrexone, which would then counteract the effects of oxycodone.

Finally, as I mentioned, ALO-02 has no visual cues that would indicate to an abuser that they have been able to successfully isolate oxycodone. This means that an abuser would have to test it on themselves in a trial and error approach. This would add a further barrier to developing successful approaches to defeat or compromise the formulation.

We designed the in vitro laboratory study program with these properties of ALO-02 in mind. The program was conducted by an independent outside laboratory that collected over 5,000 individual data points across all studies. We evaluated up to 34 different solvents in a variety of different conditions from simple to more complex. These solvents had different attributes, including polarity, ionic strength and pH, and some of these

features are described in the right-hand side of this schematic.

There were different organic solvents that included both ingestible and non-ingestible solvents. It also included readily available household solvents, solvents with different pHs as well as combinations of different solvents.

The in vitro program explored the abuse-deterrent features of ALO-02 by three of the four major routes of administration, including oral and the intravenous route as well as by smoking. To investigate abuse deterrence by the oral route, we conducted large-volume extraction studies with intact and crushed pellets in a variety of different solvents and with different conditions from simple to more complex.

The studies to address abuse by the IV route assess extraction of oxycodone and naltrexone in some volumes of different solvents using methods an abuser would do typically to prepare his opioid for abuse.

Finally, to assess deterrence to smoking,

volatilization studies were carried out with intact and crushed pellets to determine the ability to vaporize oxycodone.

The intranasal abuse potential studies with crushed ALO-02 demonstrate that the release and simultaneous absorption of oxycodone and naltrexone with insufflation as well as a reduction in the abuse potential endpoints that Dr. Roland will present shortly.

I will first share with you the large-volume extraction studies that were conducted with crushed and intact pellets in different conditions. In presenting the data, I will share extraction data from oxycodone and naltrexone obtained in these studies.

In addition, to make it possible to communicate to you the thousands of data points we developed in these studies, we've developed a so-called heat map approach as a simple graphical way to explain the behavior of the formulation in the different solvents over time across all the solvents that were studied in the large-volume

studies.

Before describing the in-vitro data, I first want to remind you of the intended design of the formulation. The first aspect of its abuse deterrence is a slow extended release of oxycodone when taken intact. This is pharmacokinetic data from the oral human abuse potential study that Dr. Roland will review shortly.

As Dr. Malhotra described earlier, with administration of intact ALO-02, you get extended release of oxycodone, shown in orange, and no measurable release of naltrexone, shown in green.

This is a profile of oxycodone release one would expect for an ER formulation when ALO-02 is taken intact that provides for the slow release of oxycodone and maintains the sequestration of naltrexone.

This represents how this looks in an in vitro extraction study. You see slow extraction of oxycodone of orange from intact pellets over time and no extraction of naltrexone, shown in green. The formulation is not compromised.

Rather, it is behaving as intended, allowing for the slow release of oxycodone, and this release is required for its analgesic benefit.

The other foundational aspect of ALO-02's abuse-deterrent properties is the sequestered naltrexone. Crushing ALO-02 is intended to cause the co-release of naltrexone with oxycodone. The bottom left panel shows what this looks like in vivo. Again, this is pharmacokinetic data from the oral human potential abuse study.

With oral administration of crushed ALO-02 pellets, you see simultaneous release and absorption of oxycodone as shown in orange and naltrexone as shown in green. It's behaving as intended with crushing.

The panel on the right is what this looks like in vitro, where you get rapid and simultaneous extraction of oxycodone and naltrexone from crushed ALO-02. With these two features of ALO-02 in mind, we've developed this heat map graphical approach for the purposes of today's presentation as a simple way to describe the behavior of ALO-02. The

times, conditions and solvents that were used in these studies were described in the closed session, and so are presented here in a blinded fashion so as not to provide a roadmap to abusers.

The two features of the formulation are reflected in this graph. On the X axis, we have percent oxycodone extraction from zero to 100 percent, and on the Y axis, we have the ratio of the percent extraction of naltrexone to the percent extraction of oxycodone. Zero is where no naltrexone is extracted, and 1 is where the percent extraction of naltrexone is equal to the percent extraction of oxycodone.

For the purposes of displaying the data, we have set cut points for both percent oxycodone extraction and the ratio of naltrexone to oxycodone extraction. For percent oxycodone extraction, the cut point is 30, and for the ratio of naltrexone to oxycodone extraction shown on the Y axis, the cut point is 0.5.

Using these cut points, we have developed a color coding that will then be used in our heat

maps. Dark green represents when oxycodone extraction is limited and less than 30 percent. The light hashed green indicates where there's effective extraction of naltrexone relative to oxycodone; that is, the ratio of naltrexone to oxycodone extraction is greater than 0.5; while the light brown shading indicates where there's reduced extraction of naltrexone relative to oxycodone.

We use this color coding to describe the behavior of the formulation over time in each solvent across all solvents tested in a specific condition. An example of the heat map is shown here.

Each column represents a different solvent while the rows represent the different time points when oxycodone and naltrexone was assessed. It is important to highlight that the brown shading indicates time points in which the naltrexone extraction is less than half of the oxycodone extraction and does not mean that there is no naltrexone present.

First, I will discuss the large-volume

extraction studies with crushed and intact ALO-02 pellets. This slide presents data from the large-volume studies with crushed pellets. The bar chart plots the percent extraction of oxycodone in orange and naltrexone in green at time point X for the 31 solvents that were tested.

The solvents are ordered according to the amount of oxycodone extracted at this specific time point. We show this time point as behavioral studies with opioid abusers indicate, that they will rarely spend longer than this trying to defeat an opioid formulation for abuse.

As you can see, there was equivalent extraction of oxycodone and naltrexone at this time point in all solvents with the exception of one solvent, solvent M27. In the inset, we show the extraction of oxycodone and naltrexone over time for solvent M27 and also for solvent MO8 which I show as an example of how ALO-02 behaves in the majority of solvents.

With M27, there was greater extraction of oxycodone versus naltrexone at all time points.

However, there was still naltrexone present which could precipitate withdrawal in dependent abusers. Moreover, this is a hazardous solvent, and additional steps would be required to isolate oxycodone for abuse.

The extraction profile with solvent MO8 is represented of the response with crushed ALO-02 in the majority of solvents, where there was simultaneous and rapid extraction of both oxycodone and naltrexone.

Finally, here we show the heat map that characterizes the behavior over time for all of the 31 solvents that were tested. This data indicates that when ALO-02 is crushed, there's simultaneous extraction in naltrexone across a variety of solvents.

This shows a similar representation of our large-volume extraction studies with intact ALO-02 pellets in condition B. As a reminder, the orange bar shows percentage of oxycodone extraction while the green bar shows percent naltrexone extraction from intact pellets for each of the different 31

solvents that were tested. Again, the solvents are ordered according to percent oxycodone extracted at the specific time point.

At time point X, you can see that there was no extraction of oxycodone in the majority of solvents tested. This is consistent with the intended design of the formulation to provide extended release of oxycodone over time.

Further, to the right, there were some solvents that showed significant oxycodone extraction, but they also showed naltrexone extraction.

In the insets, we provide representative extraction profiles for solvents on the left and those on the right. In the inset on the left, we show the extraction profile for MO8. You can see that in solvent MO8, there is very slow extraction of oxycodone in orange with no extraction of naltrexone in green.

There is some extraction of oxycodone at late time points, but this does not imply the formulation is compromised. In fact, it is just

demonstrating its extended-release mechanism.

In the inset on the right, we show the extraction profile for solvent M16. In this solvent, there was initial extraction of oxycodone, but soon thereafter, naltrexone was also extracted. Thus, there was only a short window time in which oxycodone could be extracted in the relative absence of naltrexone.

Here is the heat map for the behavior of intact ALO-02 pellets over time in all solvents tested. In the solvents on the left, extraction of oxycodone occurred at late time points from intact pellets. This is consistent with the intended extended-release properties of ALO-02, and this would be expected with all extended-release abuse-deterrent opioids and indeed is required for its analgesic benefit. With the solvents on the right, there are brief times when oxycodone was extracted, but naltrexone extraction soon followed.

It is important to recognize that these studies were done in tightly controlled conditions in the laboratory setting. In the real world where these

conditions are less well-controlled, there would be significant variability in extraction which would further decrease the likelihood that an abuser could pinpoint the perfect conditions.

A similar profile as shown for large-volume studies with a selected group of solvents in condition D, the bar chart in the top panel again shows the percent extraction of oxycodone in orange and percent extraction of naltrexone from intact pellets at time point X for these selected solvents.

As with the previous condition using our cut points to describe the behavior of the formulation, the heat map shows that there were brief periods of time in which there was reduced naltrexone extraction compared to oxycodone extraction, but this was short-lived for most solvents and the timing varied from solvent to solvent.

Additional large-volume extraction studies were carried out with intact pellets in more complex conditions. In multi-solvent extraction studies with intact pellets in different organic

aqueous solvent combinations, there were some combinations identified in which oxycodone could be extracted. Most were non-ingestible solvents, and additional steps would be required to separate oxycodone from these hazardous solvents. In all cases, there was at least some naltrexone release.

In studies with intact pellets in study condition E and condition F, potential vulnerabilities of the formulation were identified with nearly complete extraction of oxycodone with limited to no extraction of naltrexone.

In addition to the large-volume extraction studies, we also conducted small-volume extraction studies with ALO-02 to determine the potential vulnerability to abuse by the IV route. This slide summarizes the results from these studies.

The panel on the left shows oxycodone extraction in different volumes of solvent MO-1 at four different time points. Oxycodone extraction was less than 25 percent at all volumes and all time points tested.

The plot on the right shows extraction of

oxycodone in a range of different solvents at the same time point and same volume. Extraction of oxycodone was less than 20 percent in all solvents. These small-volume experiments with intact pellets demonstrate low yield of oxycodone, which would deter abuse by the IV route.

In summary, our large-volume studies with crushed pellets demonstrated simultaneous release of oxycodone and naltrexone from ALO-02 in a variety of solvents. The large-volume studies with intact pellets demonstrated that in the majority of solvents, the extended-release properties of the ALO-02 formulation was preserved.

In some solvents, there was preferential release of oxycodone, but this was dependent upon time and condition. In most conditions, there was only a brief window of opportunity before significant amounts of naltrexone was extracted which would counteract the effects of oxycodone. Further, the lower levels of naltrexone during these windows would likely lead to withdrawal in the dependent abuser.

The small-volume studies show limited extraction of oxycodone from intact ALO-02 pellets which would deter abuse by intravenous administration. Finally, the volatilization studies which were not presented today demonstrated that ALO-02 would deter abuse by smoking.

These studies demonstrated that the ALO-02 formulation shows abuse-deterrent properties in vitro. Furthermore, the lack of visual cues with this technology and fear of naltrexone would likely be a further barrier to experimentation by an abuser.

I will now introduce Dr. Carl Roland, who will describe the Category 2 and 3 data from our clinical abuse potential studies.

Applicant Presentation - Carl Roland

DR. ROLAND: Thank you, Dr. Donevan.

In addition to the Category 1 abuse potential data that Dr. Donevan has presented, I will now describe the Category 2 and Category 3 data from three studies that examine the abuse potential of crushed ALO-02 by three different

routes of abuse: oral, intranasal, and intravenous.

All three abuse potential studies were developed in cooperation with the FDA and followed the FDA guidance. The design of each of these studies was similar and consistent with other studies of abuse-deterrent formulations.

All three studies were randomized, double-blind, crossover studies in non-dependent recreational users of opioids.

The treatments are listed here, and I'll go through these as I present each study later. For all studies, ALO-02 was compared to immediate-release oxycodone and the primary measures were the drug-liking and high visual analog scales. The primary endpoint was the peak effect or Emax for an individual subjective measure. There were a number of secondary subjective measures as listed here.

The bottom of this slide illustrates the study phases used in all three studies. Each study had a screening phase to ensure subjects met the inclusion/exclusion criteria. This was followed by

a naloxone challenge phase. The naloxone challenge phase was performed to ensure that the subjects were not dependent on opioids.

After demonstration that a subject was not opioid dependent, they then entered a drug discrimination phase. The drug discrimination phase is carried out to establish that the subject can distinguish between the active treatment and placebo and that they are able to tolerate the study treatments.

The drug discrimination phase was conducted in a blinded manner. The measures used to determine drug discrimination included drug-liking, high, and take drug again. Once a subject demonstrated that they could discriminate the active treatment from placebo, they were then eligible to enter the treatment phase of the study.

This slide illustrates the primary subject measures used in all three studies, drug-liking and high, and an important secondary measure, take drug again. As recommended by the FDA guidance, drug-liking was measured by using a bipolar scale

in which zero represents strong disliking, 50 represents that they neither like nor dislike the drug, and 100 is strong liking.

The subjective measure of high was measured using a unipolar scale, where the subject reported how high they were feeling at the moment from zero representing not at all high to 100 being extremely high.

As noted in the FDA guidance, another measure of interest in these studies is the likelihood to take the drug again. This important secondary measure, take drug again, also used a bipolar scale.

After each treatment session was completed, a subject was asked if they would take this drug again. Zero represented that they would definitely not take the drug again, 50 is neutral, and 100 represented that they would definitely take it again.

The primary endpoint for each of these measures was the peak or maximum effect measured at any time after study drug was administered

described as Emax.

I will now present each of the individual abuse potential studies. As I present each study, I will discuss the study treatments and present the Category 2 data followed by the Category 3 data.

The first study is the oral abuse potential study in recreational opioid users. This study included six treatments administered in a fasted state in a crossover manner. The treatments included ALO-02 60 milligrams administered intact, ALO-02 60 milligrams crushed, oxycodone immediate-release 60 milligrams crushed, ALO-02 40 milligrams crushed, oxycodone IR 40 milligrams crushed, and placebo.

The crushed treatments were administered as a suspension. Because ALO-02 is administered intact and crushed, a double dummy was used. As noted previously, the primary comparisons were crushed ALO-02 to oxycodone IR.

This slide illustrates the Category 2 data. The oxycodone exposure over time is represented in the top panel and the naltrexone exposure over time

in the bottom panel. As seen in the top panel, there is a dose dependent increase in the oxycodone plasma concentration with both crushed ALO-02 and oxycodone IR.

When ALO-02 is taken as directed, that is, intact, represented by the dark circles, there's an extended release of oxycodone over time. The bottom panel illustrates the plasma naltrexone concentration over time.

When ALO-02 is manipulated by crushing, there is a co-release and absorption of naltrexone with more exposure to naltrexone with the higher dose. However, when ALO-02 is taken as directed, there was no measurable naltrexone represented by the dark circles at the bottom.

Of note, the median Tmax for naltrexone occurred before that of oxycodone when ALO-02 was crushed.

This slide illustrates the mean drug-liking Emax scores for the placebo and intact ALO-02 treatments relative to the oxycodone IR treatment. As demonstrated in the previous slide, the rapid

immediate release of oxycodone from the IR oxycodone treatment results in high drug-liking scores represented by the orange bar.

Taking ALO-02 intact, that is, as directed, results in an extended, slow release of oxycodone as demonstrated in the previous slide. This slow release of oxycodone translates to much lower drug-liking relative to the immediate release of oxycodone as shown here.

The mean drug-liking Emax scores for the primary comparison of crushed ALO-02 to oxycodone IR is illustrated here. The drug-liking Emax scores for both doses of crushed ALO-02 are significantly lower than the same dose of oxycodone IR.

The difference observed was approximately 16 millimeters for both doses of ALO-02. Because naltrexone is co-released with oxycodone when ALO-02 is crushed, the drug-liking response is lower compared to oxycodone by itself and oxycodone IR.

This illustrates the high Emax data from the

oral abuse potential study. Because high was measured using a unipolar scale, the Y axis goes from zero to 100 here. As seen with drug-liking, the high Emax scores for crushed ALO-02 are significantly lower relative to the same dose of oxycodone IR due to the co-release of naltrexone.

The secondary measure of take drug again is illustrated here. Again, as seen with the primary measures of drug-liking and high, take drug again is associated with lower Emax scores for crushed ALO-02 compared to the same dose of oxycodone IR.

This slide illustrates the percentage of subjects that experienced a specific reduction in drug-liking Emax for intact ALO-02 and crushed ALO-02 relative to the same dose of oxycodone IR.

The ALO-02 60-milligrams intact treatment represented by the dark blue bars resulted in 90 percent of subjects experiencing at least a 30 percent reduction in drug-liking relative to oxycodone IR 60 milligrams, and 87 percent of subjects experienced at least a 50 percent reduction in drug-liking.

With crushed ALO-02, either 40 or 60 milligrams, we saw that at least 61 to 65 percent of subjects experienced at least a 30 percent reduction in drug-liking while 45 to 55 percent of subjects experienced at least a 50 percent reduction in drug-liking relative to oxycodone IR.

I will now present the intranasal abuse potential study. This study included four treatments administered in a fasted state in a crossover manner. The treatments included ALO-02 30 milligrams administered crushed, oxycodone IR 30 milligrams crushed and matching placebos. ALO-02 was matched by weight to placebo sugar spheres, and oxycodone IR was matched by weight to placebo lactose tablets.

As with the oral abuse potential study, the primary comparison was crushed ALO-02 to oxycodone IR.

The Category 2 data are illustrated here with the oxycodone exposure over time in the top panel and naltrexone exposure over time in the bottom panel. As seen in the oral abuse potential

study, there is co-release and absorption of oxycodone and naltrexone with crushed ALO-02 when administered intranasally.

The drug-liking Emax data from the intranasal abuse potential study is shown here. As expected, the placebo treatments were similar to each other and lower than the ALO-02 or oxycodone IR drug-liking Emax scores.

The drug-liking Emax score for crushed ALO-02 is significantly lower than crushed oxycodone IR, again due to the co-release of naltrexone. The difference here was large, 33.4 millimeters.

This is the secondary measure of take drug again. As seen with drug-liking, the take drug again Emax score for crushed ALO-02 is significantly lower than oxycodone IR. The take drug again response to ALO-02 was not significantly different from the placebo response.

This is the responder analysis for the intranasal abuse potential study. Crushed ALO-02 30 milligrams resulted in 93 percent of subjects

experiencing at least a 30 percent reduction in drug-liking relative to oxycodone IR, and 85 percent of subjects experienced at least a 50 percent reduction in drug-liking.

I will now present the final abuse potential study that was conducted, the IV abuse potential study. This study included three treatments administered in a fasted state in a crossover manner. Please note, consistent with the FDA guidance, crushed ALO-02 was not used in this study for concerns of safety in this healthy volunteer study.

The treatments included a simulated parenteral dose of ALO-02 20 milligrams administered as oxycodone 20 milligrams for injections and 2.4 milligrams of naltrexone for injection, oxycodone 20 milligrams for injection as the active control, and normal saline was used as the placebo treatment.

The Category 2 data demonstrate, as expected, that there was immediate exposure of oxycodone and naltrexone when administered

intravenously. As seen in the intranasal study, the difference in the drug-liking Emax scores for simulated ALO-02 and oxycodone are large, approximately 34 millimeters. This was statistically significant.

As seen with drug-liking, the take drug again Emax scores for simulated ALO-02 are significantly lower than oxycodone. This difference was also large, approximately 31 millimeters and similar to the difference seen in the intranasal study. The placebo response to take drug again was similar to simulated ALO-02.

The responder analysis for the IV abuse potential study demonstrates that simulated ALO-02 20 milligrams resulted in 90 percent of subjects experiencing at least a 30 percent reduction in drug-liking relative to oxycodone, and 83 percent of subjects experienced at least a 50 percent reduction in drug-liking. These results are similar to those seen in the intranasal abuse potential study.

To summarize the abuse-deterrent studies,

the Category 1 and 2 data demonstrate that crushing ALO-02 results in a simultaneous release and absorption of oxycodone and naltrexone. These data combined with the Category 3 data demonstrate that ALO-02 has abuse-deterrent properties following manipulation and administration by the oral and non-oral routes.

Dr. Donevan will now come back to provide some concluding remarks on behalf of Pfizer.

Applicant Presentation - Sean Donevan

DR. DONEVAN: So to summarize what you've heard here today, the ALO-02 NDA was a 505(b)(2) submission and referenced Roxicodone and Revia. The development program consisted of nine clinical studies and an extensive number of in vitro studies to support the abuse potential properties of ALO-02.

The clinical pharmacology studies support that with ALO-02, the bioavailability is equivalent to Roxicodone. It has a pharmacokinetic profile that supports twice-daily dosing and can be taken with or without food. Finally, ethanol does not

cause dose dumping.

The two efficacy and safety studies demonstrated that ALO-02 has efficacy that is superior to placebo in patients with chronic low back pain and demonstrated the long-term safety and maintenance of ALO-02's efficacy in chronic non-cancer pain.

Importantly, the abuse-deterrent studies demonstrate that ALO-02 has reduced abuse potential by all three routes of administration.

In conclusion, the safety and efficacy of ALO-02 has been demonstrated in chronic pain. The in vitro and pharmacokinetic data demonstrate that when ALO-02 is crushed, there is simultaneous release and absorption of both oxycodone and naltrexone. The Category 3 data further support the reduced abuse potential of ALO-02 when manipulated and administered by the oral, intranasal and intravenous routes.

Overall, the evidence that we have provided today supports abuse-deterrent labeling for ALO-02. Pfizer agrees that a multifaceted approach

involving multiple stakeholders is essential to address the complex and critical problem of prescription opioid abuse. We believe that ALO-02 is an important step towards this goal of creating safer opioid analgesics.

Thank you for your attention and for the opportunity to present ALO-02 to you today.

Clarifying Questions

DR. BROWN: Thank you.

Are there any clarifying questions for the folks at Pfizer? Please remember to state your name prior to asking your question for the record. If you can, please direct your questions to a specific presenter.

We'll start with Dr. Emala.

DR. EMALA: Hi. Charles Emala. I have questions on two slides, I think, for Dr. Donevan, slide 45 to start with.

DR. DONEVAN: Could we see slide 45, please?

DR. EMALA: So I'm curious. For solvent 27, when the extraction exceeds the selected cutoff points, how thoroughly it exceeds those cutoff

points. I'm curious, at the earlier time points in 27, if we know how thoroughly extracted the oxycodone is and how low the ratio of oxycodone and naltrexone is.

Related question and I'm not sure if this is part of the FDA guidance, but recognizing that this is a harsh organic solvent, I'm curious as to whether consideration of simple evaporation of the solvent is considered part of these studies.

DR. DONEVAN: So maybe while they're conferring, maybe I can address the extraction of solvent M27. You see the heat map in solvent M27. The extraction profile that shows extraction of naltrexone and oxycodone over time is shown in the inset in the upper left.

You can see that at early time points, you have reduced oxycodone extraction as well as reduced naltrexone extraction. With increasing durations of exposure, you see increase in extraction of both oxycodone and naltrexone. But at all time points, the extraction of oxycodone is greater than that of naltrexone.

DR. EMALA: Can I ask a related question?

DR. BROWN: Absolutely.

DR. EMALA: On slide 48, for solvents 16 and 23, we're now looking at ingestible solvents. And my question is similar. When the cutoff is exceeded at these early time points, do we know by what margin they're cut off at? It's somewhat reassuring that at later time points naloxone seems to catch up. I would assume that these cutoffs are being just marginally exceeded at these early time points.

DR. DONEVAN: So I think you're referring to solvent M16, correct?

DR. EMALA: Yes.

DR. DONEVAN: Again, if you look at solvent M16 in the heat map, you see that there are two time points where there's reduced extraction by naltrexone. That is, it's less than 0.5 of the extraction of oxycodone as well as oxycodone extraction, that it exceeds 30 percent.

Immediately after that time point, the extraction of naltrexone is at least 50 percent of

the extraction of oxycodone, and then over time -- and you can see that in the inset on the right -- you get complete extraction of naltrexone.

DR. EMALA: Thank you.

DR. BROWN: Dr. Morrato?

DR. MORRATO: My question also relates to the slide MO-48.

DR. DONEVAN: Can we have that slide, please?

DR. MORRATO: It has to do with this -- this kind of helps us maybe.

DR. DONEVAN: Did you say slide 48? I don't think we heard --

DR. MORRATO: Yes. Sorry. Because it relates to how we are defining the thresholds.

DR. DONEVAN: Yes.

DR. MORRATO: Could you explain for us in the open session how those were clinically defined or justified and what sensitivity analysis? So I'm looking at the curves on the bar chart at the top there and that's final extract percent or is that at certain time points?

DR. DONEVAN: It's a percent extraction at certain time points.

DR. MORRATO: But the bar charts that you have above the solvents, that's the endpoint?

DR. DONEVAN: That's the specific -- so essentially, each row represents a single time point over the --

DR. MORRATO: Not each row, the bar charts that you have --

DR. DONEVAN: Right, yes.

DR. MORRATO: -- above this one.

DR. DONEVAN: Yes, that represents the percent extraction of naltrexone and oxycodone specifically at that time point X.

DR. MORRATO: Time point X is what?

DR. DONEVAN: So which is highlighted in the brown.

DR. MORRATO: What? The one-hour mark.

DR. DONEVAN: Yes.

DR. MORRATO: Okay. Yes. Now I understand. So you've picked that as a threshold.

But I can look at the bar charts, and I know

you're using, like, a 50 percent ratio. And they're looking like they're hovering around that cut. I'm trying to understand, one, the justification for that cut and if you've done histograms that are looking at are we picking a point in the middle of a peak that's right around 0.5, or is this really -- how well is it discriminating, I guess?

DR. DONEVAN: Yes. We can talk about that. If we could have slide IV-40, this was the rationale for developing the cut points. There's really no validated cut points that have been identified in this scientific literature. We developed these simply for the purposes of showing the behavior in a large set of experiments that we've conducted.

In terms of the percent oxycodone extraction of 30 percent, we developed that based on the understanding that if you look at Cmax for ALO-02 comparing crushed to intact or if you compare IR oxycodone compared to intact ALO-02, the Cmax is roughly 30 percent of the crushed product or IR

oxycodone. It seems to be similar to how the oxycodone release would occur with intact product.

For the oxycodone extraction cut point of 0.5, the naltrexone oxycodone extraction of 0.5, we developed that based on some dose-modeling work that we had done with oxycodone in different ratios of naltrexone. So that's shown on the plot on the right.

This was developed using the data with ALO-02 as well as some data with other combinations of opioids and naltrexone. We constructed the model, and the model shows the data on the right. You can see on the Y axis is the percent maximal reduction in drug-liking, and on the X axis are different increasing concentrations of naltrexone compared to oxycodone.

It's an increase of the concentration of naltrexone to oxycodone. You see an increase in reduction in drug-liking.

Now, the 12 percent which represents ALO-02 is near maximal reduction in drug-liking. If you decrease that 12 percent by half, which would be

equivalent to getting 50 percent less extraction of naltrexone, you still achieve at least 60 percent of the maximal reduction in drug-liking.

We consider that that naltrexone would still be effective at reducing drug-liking with the extraction ratio that was 0.5 or above. With 0.5 or below, naltrexone would be less effective at reducing drug-liking. However, if you were a dependent abuser, for instance, it's likely that less than 0.5 naltrexone would still be effective at reducing drug-liking as well as potentially precipitating drug withdrawal because they tend to be more sensitive to the effects of naltrexone.

DR. MORRATO: So have you done sensitivity analyses on two parameters, one is this is choosing the drug-liking score, and you could also be looking at the will I take again score, as well as variation around the 0.5.

DR. DONEVAN: Yes. This was constructed looking at drug-liking. I don't know that we've developed a model with take drug again. My guess is it would look quite similar because the

drug-liking reductions parallel the reductions in drug-liking.

We have done sensitivity analysis with heat maps where we've changed the cut points. So I'll show one example, which is IV-44.

In this example, what we have done is we've changed the cut point for oxycodone extraction from 30 percent to 20 percent. The 30 percent was what I showed you in the main presentation on the top. I'm sorry. I'm looking at the wrong screen. This is the data with intact pellets that I presented.

You can see that, with changing the cut point to 20 percent, there are only minor changes in the behavior of the formulation. You can see that reflected in comparing the top, which was the 30 percent cut point, and the bottom, which was the 20 percent cut point.

DR. MORRATO: How about variation around the 0.5?

DR. DONEVAN: We looked at that, too. That's IV-45, please. This is where we elevated the ratio from 0.5 to 0.75, and again, this is the

large-volume study with intact pellets, condition C. The top panel is what I showed in the open presentation with a cut point of 0.5, and the bottom panel is the cut point of 0.75.

Again, as you saw with changing the oxycodone extraction cut point, there were fairly modest or small changes in the profile if one increases the requirement for naltrexone to oxycodone extraction.

DR. MORRATO: So these are looking at if I'm reading it, if it's going above -- if it's 0.75, you're preferentially extracting naltrexone over the oxycodone, correct? Am I interpreting that right?

DR. DONEVAN: Above 0.5 means you have at least 50 percent extraction of naltrexone compared to oxycodone. 0.75 means you have 75 percent naltrexone extracted to oxycodone extracted.

DR. MORRATO: Right, so they're preferentially --

DR. DONEVAN: It's becoming more and more conservative going from 0.5 to 0.75.

DR. MORRATO: What if you're looking at it the other way and I'm wanting to look at -- do you have the ratio where it's less than 0.5?

DR. DONEVAN: If we lowered it, I'm less concerned --

DR. MORRATO: So I'm selectively getting more of the oxycodone extracted out than I'm getting of the naltrexone. Is that what the ratio is capturing?

DR. DONEVAN: So just to reiterate, going from 0.5 to 0.75 is a more conservative criteria, okay? It means you need more naltrexone to reach a beneficial effect using that cut point. This is a more conservative cut point. If we lower the ratio of naltrexone to oxycodone extraction, meaning you require less naltrexone to oxycodone -- I believe we have that.

DR. MORRATO: Also, do you have the same data with the crushed pellets, not just the intact?

DR. DONEVAN: We have looked at crushed pellets, and I don't know that I have that right now. But we can develop that for you for later

this afternoon and address that.

DR. MORRATO: The reason I'm asking this is trying to wrap my mind around the statement that's in the FDA's briefing book which says, "Oxycodone is selectively extracted from intact pellets by a number of straightforward techniques, and common solvents appear to be capable of removing naltrexone selectively from crushed."

So that's why I'm trying to understand these data relative to these other statements.

DR. DONEVAN: Yes. So maybe if we go back to the open presentation -- let me find the specific slide. I'm sorry. Could we have the open presentation with intact pellets heat map, please? Sorry. Crushed is what she requested.

This shows the heat map for crushed pellets. I already went through with you solvent M45. Thank you. So this was the heat map that we showed in the open presentation.

You can see that solvent M27 is highlighted in the brown shading in the heat map, and then you can see solvent M27, the actual extraction profile

from which this heat map was developed for M27 in the upper left, okay? That's really the outlier. The majority of solvents behave like solvent MO8, where there was rapid and complete extraction of naltrexone and oxycodone from crushed pellets.

If you look further on the left of the bar chart for solvents M24, and M11, and M25, you see that there was very little extraction of either oxycodone or naltrexone in these solvents, and that was maintained through the duration of the extraction study. So a few showed no extraction, most showed complete extraction of oxycodone and naltrexone, and then we had solvent M27.

DR. MORRATO: Okay.

DR. DONEVAN: There were two other solvents. Just to show you two final examples, which would be IV-46, which is really just showing you what I just described for you, but we'll show it anyway, IV-46.

DR. BROWN: Is it coded?

DR. DONEVAN: Hmm?

DR. BROWN: Is IV-46 coded?

DR. DONEVAN: Yes, it's coded. Thank you

for reminding me.

If we can have IV-46, thank you. Again, this just describes solvent M11 and solvent M25 that I showed you previously. With solvent M, there was no extraction of either oxycodone and naltrexone across the duration of the study.

In solvent M25, you can see that with this specific solvent, there was actually an increase in extraction of naltrexone over oxycodone.

DR. MORRATO: Okay. Can I just ask one related to it? Is that okay timewise?

DR. BROWN: Yes.

DR. MORRATO: The FDA also says that a common solvent under stress conditions, right? None of these heat maps are under stress conditions, correct, like temperature, agitation?

DR. DONEVAN: We have provided heat maps under different stress conditions. If we show the open-session slide -- sorry, yes, this one -- this was under stress conditions, yes. MO-49, please.

This was under stress conditions. You can see that with some solvents, there was very little

extraction of either oxycodone and naltrexone across the duration of the studies. With other solvents, there was some extraction late, but that's expected because it is an extended-release opioid, and with some solvents, there was extraction earlier, but it was then followed by naltrexone.

DR. MORRATO: Okay. Just to clarify then, the abuse potential studies are only using the physical manipulation and did not test any of these chemically-manipulated products, correct?

DR. DONEVAN: The oral study looked at crushed ALO-02. That crushing was done with mortar and pestle. It also looked at intact ALO-02 pellets that were swallowed intact.

The intranasal study was done with crushed ALO-02 again using mortar and pestle. Then the IV study used a simulated crushed ALO-02 with the same ratio of naltrexone to oxycodone.

DR. MORRATO: Yes, physical manipulation.

DR. DONEVAN: Yes.

DR. MORRATO: Then you make a statement, I

think it's slide -- this is my last point.

DR. DONEVAN: Sure.

DR. MORRATO: MO-53, I guess, something that the fear of naltrexone is likely to limit extensive experimentation. I'm wondering if you could share the data to justify that statement.

DR. DONEVAN: Sure. I can refer to some of the chatroom data with Embeda, and then actually, I'd like to turn it over to Dr. Edward Sellers to comment.

DR. BROWN: Actually, I would like to defer this discussion until after the FDA has had an opportunity to give their presentation because I believe it will give us a better chance to have an understanding of what the issues really are. I'm certain that we're going to want to come back to this.

We're going to take a break now, and we'll come back at 11:15. Please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience.

(Whereupon, at 11:05 a.m., a recess was taken.)

DR. BROWN: We're now going to proceed with the FDA presentations.

FDA Presentation - Joann Lee

DR. LEE: Hello, everyone. I'm Joann Lee, drug utilization data analyst in the division of epidemiology, Office of Surveillance and Epidemiology. I'll briefly present the drug utilization patterns for oxycodone extended-release and other extended-release or long-acting opioid analgesics from 2011 through 2015 to provide context for today's discussions.

I'll describe the sales distribution of extended-release opioid products followed by prescription utilization of oxycodone extended-release and other opioid analgesics focused on the outpatient retail settings. I'll then present our findings on the top prescriber specialties for oxycodone ER and finish with limitations and summary.

We'll focus on oxycodone extended-release

because the drug in discussion today involves oxycodone-containing combination product oxycodone and naltrexone or Troxyca ER.

We also looked at other extended-release or long-acting opioid products as shown on this slide, which is the opioid market into which the drug being discussed today will be introduced to, if approved. This opioid market includes oxycodone, methadone, morphine, hydromorphone, oxymorphone, tapentadol, hydrocodone, and the transdermal patches fentanyl and buprenorphine.

To determine the primary settings of care, we used the IMS National Sales Perspectives database to provide the sales distribution data of oxycodone extended-release and other extended-release or long-acting opioid products that were sold from manufacturers and wholesalers into the various settings of care.

Please do note these sales data are nationally projected to all settings of care.

As displayed in this chart, 75 percent of oxycodone extended-release products were

distributed from manufacturers to retail settings, and additionally, the majority of each of the other extended-release or long-acting opioid products that I just described and included in this review were also distributed to the retail settings. Based on these sales data, we focused on the U.S. outpatient retail pharmacies.

For the prescription data analysis that I'll present next, we used the IMS Health National Prescription Audit database. This measures the dispensing of prescriptions from retail pharmacies into the hands of consumers through prescriptions within the United States. These prescription data can also be stratified by prescriber specialty.

So to show our findings, this figure presents the nationally estimated number of prescriptions dispensed for oxycodone extended-release as shown by the green line, and the remaining lines represent the other extended-release or long-acting opioid analgesic prescriptions which were dispensed through the U.S. outpatient retail pharmacies from 2011 through

2015.

The total number of prescriptions dispensed for oxycodone extended-release decreased by 24 percent from approximately 5.8 million prescriptions in 2011 to 4.4 million prescriptions in 2015.

This chart shows the top prescribing specialties for oxycodone extended-release in 2015. Over one-quarter of oxycodone extended-release prescriptions were written by family practice, general practice, and osteopathy followed by internal medicine, nurse practitioner, and anesthesiology at 11 percent each and so on. Pain medicine accounted for 5 percent of prescriptions written for oxycodone extended-release in 2015.

Please to keep in mind that only outpatient use was assessed, that is, inpatient and mail-only data were not included in our analysis. Top specialties that prescribed oxycodone extended-release were captured as reported by the prescription data.

So to summarize, there was a decrease in

utilization of oxycodone extended-release by 24 percent from 2011 through 2015. Of the extended-release or long-acting opioid market, oxycodone extended-release was the third most frequently dispensed drug, with 4.4 million prescriptions dispensed in 2015.

The top prescriber specialties were again, family practice, general practice, and osteopathy for the year 2015.

Dr. Kilgore will discuss the labeling issue next. Thank you.

FDA Presentation - Elizabeth Kilgore

DR. KILGORE: Good morning. My name is Elizabeth Kilgore, and I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products.

This morning, I will be presenting the following topics related to the proposed abuse-deterrent labeling, drug abuse classwide abuse language, risk specific to abuse of Troxyca ER, abuse deterrence testing, abuse potential endpoints, types of studies, and summary.

The extended-release long-acting opioids as a class contain the following language about abuse potential. This same language will be included in the label for Troxyca ER. Troxyca ER contains oxycodone, a substance with a high potential for abuse similar to other opioids, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxymorphone.

Troxyca ER can be abused and is subject to misuse, addiction and criminal diversion. The high drug content in the extended-release formulations adds to the risk of adverse outcomes from abuse and misuse. All patients treated with opioids require careful monitoring for signs of abuse and addiction.

In addition, the following information in the label is more specific to Troxyca ER. Taking chewed, crushed, or dissolved Troxyca ER enhances drug release and increases the risk of overdose and death. If the capsules are crushed or chewed, up to 100 percent of the sequestered naltrexone hydrochloride dose could be released.

In opioid tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal and, due to the presence of talc excipient, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

You have heard about the in vitro laboratory studies that were done to explore the different methods that might be employed to defeat the extended-release and the abuse-deterrent properties of Troxyca ER.

The following statements in the label will summarize the results of those in vitro studies. In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When Troxyca ER is crushed and mixed in a variety of solvents, both oxycodone hydrochloride and naltrexone hydrochloride are simultaneously extracted.

You have also heard about the three human

abuse liability studies that were performed with Troxyca ER. The first explored the potential for oral abuse, and the second explored the potential for intranasal abuse. A third study was conducted with IV administration of simulated crushed Troxyca ER.

Many different endpoints may be used to measure human abuse potential outcomes. The agency feels that take drug again with support from drug-liking is the most clinically relevant endpoint in the context of evaluating the potential for abuse deterrence because this endpoint reflects the willingness of an abuser to take the drug again.

A purported abuse-deterrent product may have a slightly lower drug high compared to a non-abuse-deterrent comparator, but a more important indicator of the abuse-deterrent potential of the product is whether the abuser is willing to take the drug again.

The results for the following two endpoints, take drug again and drug-liking, will be summarized

in the label for the studies. Take drug again was measured on a bipolar 100-point visual analog scale where zero represents strong negative response, definitely would not take drug again, 50 represents a neutral response, and 100 represents the strongest positive response, definitely would take drug again.

Drug-liking was measured on a bipolar 100-point visual analog scale where zero represents maximum disliking, 50 represents a neutral response, neither like nor dislike, and 100 represents maximum liking.

The next three slides summarize the proposed labeling to describe the oral abuse potential study. As you heard, in a randomized double-blind active and placebo-controlled study, 31 non-dependent recreational opioid abusers received all six of the following treatments by the oral route, as shown.

Oral administration of crushed 40-milligram Troxyca ER was associated with statistically significant lower means and medians for drug-liking

and take drug again compared with crushed 40-milligram IR oxycodone hydrochloride and statistically significantly lower means and medians for drug-liking in Troxyca ER 60 milligrams compared to crushed 60-milligram IR.

The summary statistics are shown in the following table. This table will be included in the label and summarizes the results from the treatment groups. Note that the mean take drug again for the crushed Troxyca ER, 40 milligrams, is approximately 57, which is less than the 40 milligrams immediate-release oxycodone mean of approximately 83.

The mean take drug again for crushed Troxyca ER, 60 milligrams, is approximately 71, which is less than the 61 milligram immediate-release crushed oxycodone mean of approximately 81. A similar pattern is seen for the means of drug-liking. Also, I should point out that the boxes in these tables and figures are for presentation purposes only and will not appear on the label.

This figure will be included in the label to

summarize the present reduction in drug-liking for crushed Troxyca ER compared to the immediate-release oxycodone. The Y axis represents the percent of subjects obtaining the percent reduction greater than or equal to the value on the X axis.

For example, about 74 percent of the subjects experience some reduction in drug-liking with the 40-milligram crushed Troxyca ER, and 77 percent experienced some reduction in drug-liking with 60 milligrams of Troxyca ER compared to IR oxycodone.

Sixty-five percent of subjects using Troxyca ER, 40 milligrams, had at least a 30 percent reduction, and 61 percent of Troxyca ER, 60 milligrams, had at least a 30 percent reduction in drug-liking compared to oxycodone IR of the same doses.

Fifty-five percent of 40 milligrams and 45 percent of 60 milligrams had at least a 50 percent reduction in drug-liking compared to crushed oxycodone IR at the same doses.

The next three slides summarize the proposed

labeling to describe the intranasal abuse potential study. As you heard, in a randomized double-blind active and placebo-controlled study, 27 non-dependent recreational opioid abusers with experience with intranasal administration of opioids received all four of the following treatments by the intranasal route as shown.

Intranasal administration of crushed Troxyca ER was associated with statistically significantly lower means and medians for drug-liking and take drug again compared with crushed IR oxycodone hydrochloride.

The summary statistics are shown in the following table. This table will be included in the label and summarizes the results for four intranasal treatment groups. Note that the mean take drug again for crushed Troxyca ER is 58, less than the immediate-release crushed oxycodone mean of 88. A similar pattern is seen for the means of drug-liking.

This figure will be included in the label to summarize the percent reduction in drug-liking for

Troxyca ER compared to the immediate-release crushed oxycodone. The Y axis represents the percent of subjects attaining a percent reduction greater than or equal to the value on the X axis.

For example, 93 percent of subjects experienced some reduction in drug-liking Emax with 30 milligrams crushed Troxyca ER compared to crushed IR oxycodone. For 93 percent, the reduction was 30 percent or more. For 83 percent, the reduction was 50 percent or more.

The study in non-dependent recreational opioid abusers compared 20-milligram IV oxycodone hydrochloride in combination with 2.4-milligram IV naltrexone hydrochloride to simulate parenteral use of crushed Troxyca ER to 20 milligrams of IV oxycodone hydrochloride and placebo. Twenty-nine subjects received all three treatments.

Intravenous administration of oxycodone and naltrexone showed statistically significantly lower mean and median drug-liking and take drug again Emax scores. Drug-liking median score was 51 for Troxyca ER compared to an oxycodone-alone median

score of 97. Take drug again median score was 50 for Troxyca ER compared to oxycodone alone, where the median score was 81, and 90 percent of subjects experienced some reduction in Emax of drug-liking with simulated parenteral use of crushed Troxyca ER compared to IV oxycodone.

This summary of the abuse-deterrent properties of Troxyca ER will appear at the end of section 9.2 of the label. The in vitro and pharmacokinetic data demonstrate that crushing Troxyca ER pellets results in a simultaneous release and absorption of oxycodone hydrochloride and naltrexone hydrochloride. These data along with results from the oral and intranasal human abuse potential studies indicate that Troxyca ER has properties that are expected to reduce abuse via the oral and intranasal routes.

However, abuse of Troxyca ER by these routes is still possible. Additional data, including epidemiological data when available, may provide further information on the impact of the current formulation of Troxyca ER on the abuse liability of

the drug.

A human abuse potential study of intravenous oxycodone hydrochloride and naltrexone hydrochloride to simulate crushed Troxyca ER demonstrated lower drug-liking and take drug again Emax compared with oxycodone hydrochloride alone. However, it is unknown whether these results with simulated crushed Troxyca ER predict a reduction in abuse by the IV route until additional postmarketing data are available. Thank you.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for the FDA? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Let me say that there are many questions for the folks at Pfizer, and we're going to address those after lunch and after the open public hearing. We'll get all those questions answered at that time, but any clarifying questions for the FDA?

Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. The first is just really a request. Could somebody at FDA maybe provide a crosswalk for the two different coding schemes regarding the solvents? Because otherwise, I think any discussion will be incredibly difficult unless we have some savants in the audience, between the two different coded schemes, just so we know what L means in the M, some kind of a crosswalk. That would be great, I think.

DR. HERTZ: Let me see what we can do. Once we have a chance to break, maybe we can just do that --

DR. GERHARD: That's good.

DR. HERTZ: -- and just give you the table of X equals Y and J equals K, that kind of thing.

DR. GERHARD: Exactly.

Two quick questions, one regarding this kind of summary statement that additional epidemiological data would obviously help us understand what the real-world impact of these

approaches is.

In this case, we have with Embeda a product that uses the same approach, has been on the market for a while. Do we have any epidemiological data that would inform what the real-world impact on the abuse potential is?

DR. HERTZ: We don't have the data yet, and I think what's important is to note is that while Embeda has been approved for a long time, perhaps the company can describe the actual marketing periods because it has been present on the market for a much shorter period than one would think based on the different approval dates.

So it actually hasn't been out for very long and circulating. I think we also saw that the distribution was not very high, and really, to get meaningful data from postmarketing epi evaluations, it's difficult without having more market penetration.

DR. GERHARD: Then one last question to slide 8 in the last presentation of Dr. Kilgore, this looks at the oral abuse potential when we look

at the take again score which was kind of highlighted as maybe one of the more meaningful measures here.

We see what I think at least what I would describe as an unexpected dose effect where for the 40 milligram formulation crushed, the drug-liking is much closer to the 50 percent mark than it is for the 60-milligram formulation, although in a sense, I would have expected that the greater volume of naltrexone would have made up for that

Where the 71 for the 60-milligram -- in that context, I find it a bit concerning, and maybe you can clarify whether it was done or why it wasn't done, that we don't see data for the 80-milligram because, obviously, these are two data points from small samples. But if you just extrapolate what you see here, you'd find something that maybe wouldn't have a meaningful difference anymore to the IR oxycodone at the 80-milligram level.

DR. HERTZ: I'm not aware that the 80-milligram was done. I see heads shaking behind you.

I guess as you consider the meaning of the data, the implications of the data, you can think about it assuming that there is or isn't an effect and how that influences your thinking as you go forward.

DR. BROWN: Dr. Emala?

DR. EMALA: More of a comment than a question for Dr. Kilgore, slide number 5. I think the second -- my understanding is this is intended labeling language that would be included with the product, and I think bullet point number 2 is a little bit of an overstatement. While I think it's true for most solvents at most time points, I don't think it's exclusively true.

My only suggestion would be that that statement probably needs to be softened a little bit.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. This goes back for Dr. Lee, what we had talked about yesterday, too, in terms of the prescriber data where again, this time, family practice were

primary at 26 percent. But again, anesthesiologists, generally probably, I would include within the pain medicine category again because as we were saying, usually the anesthesiologists that are prescribing retail oxycodone ER usually are pain guys or girls.

DR. STAFFA: This is Judy Staffa. I think as we discussed yesterday, that's probably the case, but the data come from prescribers reporting their specialty to AMA and then those files are linked. I would guess your comment is absolutely correct.

DR. BROWN: Dr. Gupta?

DR. GUPTA: Yes. I had a question about slide 8. I believe Toby has already asked it, so I'm going to pass on that, but I did have a concern on whether or not higher doses were evaluated above 60 milligrams.

Then the other question I had was about the summary statement, bullet number 1, regarding the crushing of the medication into the pellets and the fact that there's simultaneous release and

absorption of both oxycodone and naltrexone. Do you have any information as it relates to the extraction data that we discussed earlier specifically with solvent 27 or any comment on that?

DR. HERTZ: Are you asking the sponsor?

DR. GUPTA: I'm asking anyone, I guess. I don't know if FDA can respond, but there was no discussion. It states that if you crush, yes, of course, there's simultaneous release. But, demonstrated earlier in the data that was presented, there was a solvent specifically where we saw there wasn't simultaneous release.

So unless I'm misunderstanding the data that was presented, I was just wondering, is there a comment on behalf of the FDA as to how relevant that information is regarding the fact that there wasn't simultaneous release?

DR. HERTZ: I think that we are listening to the comments about the way we've conveyed it, and we will certainly take another look at it. We heard one comment that it seems to be overstated so

we'll go back and look at that language and yours.

DR. BROWN: Dr. Morrato?

DR. MORRATO: Yes. Related to that because it looks like it's the same labeling language that's in the Embeda, presumably also because it's using the same kind of platform, so can you share, since it wasn't publicly reviewed, were the original in vitro studies similar in what you saw with the Embeda platform? In other words, what we're seeing here is consistent with what you would expect with a naltrexone abuse-deterrent strategy.

DR. HERTZ: In a very general sense, I believe, yes. I can't bring the Embeda to mind at this moment, but I do believe we did take a look at the application where we were doing the review to see how things compared. It was a while ago, but usually, we will go back just to see relative just for our own understanding. But yes, I'd have to go back and take another look to confirm it.

I mean, we saw the comparisons from the company of what was done, so I know that there are more data from this evaluation, but I'd have to go

back one more time to compare the outcomes.

DR. MORRATO: I would just hope that if there's discussion around how to soften the language appropriately, there might be carryover into the other labeling for consistency just because it's using the same -- yes.

DR. HERTZ: Good point. Noted.

DR. BROWN: Dr. Winterstein.

DR. WINTERSTEIN: That goes back to the earlier discussion about are there solvents that differentially release or don't they, the discussion that Dr. Morrato started just before the break. We were thinking that the FDA might address this more clearly.

Now we have this statement here that would suggest that the FDA feels there is not that step differential extraction, at least when looking at this statement. I wanted to offer perhaps an interpretation of this, if we could bring up that sponsor slide again, MO-48, because I think the main issue in looking at the ability to differentially extract oxycodone versus naltrexone

is really a function of the solvent, but more so a function of time.

It's not so much about the sensitivity analysis with these thresholds or the manipulation. It's just a matter of time, and if we have that slide real quick --

DR. BROWN: Excuse me. Could we get MO-48?

DR. WINTERSTEIN: No?

DR. BROWN: We'll get it for you. I think it's important that we look at that.

DR. WINTERSTEIN: I think that visually, to me, it makes it fairly clear. So there's this bar chart on the top that's essentially the reflection of time point X, which is this big old bar in this heat map. If we move that horizontal bar down two time points, we have four solvents that extract preferably oxycodone and not naltrexone, and they do this in a sustained fashion so you can wait longer and you get the same.

So there is not that magic time point like in those solvents to the right where there is just a short time period where more oxycodone is

extracted and less naltrexone in those four solvents that I'm looking at. That would be M21, M22, M15 and M27. All those differentially extract oxycodone and not so much naltrexone if I wait long enough.

DR. BROWN: That's interesting. Could you expand on that a little bit as it would relate to an abuser and the likelihood that they would be able to create a circumstance where they could break down the abuse deterrent?

DR. WINTERSTEIN: It's just a matter of interpreting the heat map. So this black bar of time point X is essentially arbitrarily choosing, right? So if I don't use the time point X, but I wait a little bit longer and, since we cannot release what time point X is, we cannot release what is underneath there, but if we assume that these are half-an-hour increments, if I wait longer, then I get what I want which would be a good amount of oxycodone and not so much naltrexone.

There are clearly scenarios, and this is not

with heat manipulation. This is even not crushed. This is simply throwing the pellets into a solvent and waiting for some time.

So everything that's brown is what we don't want to see, and there are four solvents that have brown bars that start basically one time point after the one that is chosen right now to illustrate. So that bar chart that we have on the top would look very different, if we move that horizontal line two steps down, would show us an extraction of oxycodone that is more than 30 percent and a ratio of naltrexone to oxycodone that is less than 0.5, if I interpret this correctly.

DR. BROWN: Thank you, Dr. Winterstein.

I'd like to ask the FDA if they could help us. Is it reasonable to assume that this is the reason for a large difference between the information that we -- or the interpretations by the FDA that we received before this meeting and the interpretations that we heard today?

DR. HERTZ: I'm not sure I understand that there is a big difference. I think that, when we

think about what to put in a label, we obviously don't put it all in because that would be pages and pages of data.

I think what we try to do was represent the data -- was provide a summary of the data most representative of what we think the behavior's likely to be out in the community with regard to abuse, and then where if we think that that activity has been impacted some way by the formulation and we think that the impact is sufficient to concur that there may be some abuse-deterrent properties, then that's what we will convey.

The question about intact versus crushed and the different solvents used in the different settings is difficult to always understand how much that behavior will represent -- the novel approaches in which these products can be defeated that are pushed in the stress conditions of the testing almost invariably for every formulation will show some ability to defeat it.

If you put the effort in, you're going to

get what you want out because, again, as we've said before, the opioid has to be able to be delivered in order for the product to be an analgesic.

So we try to weigh where we think the data are consistent with behavior that's more common or less difficult and where more sophisticated methods, thinking, approaches have to occur. So what we put in the proposed language here is where we thought the balance might adequately represent the findings.

I'm hearing perhaps some differences from the committee so that's part of having the meeting, to hear this. So I don't think that there's a disagreement in the data. We have a mismatch on the coding, but aside from that, I think the differences in the information provided and the labeling presented are about decisions on what to include in the label.

DR. BROWN: Thank you, Dr. Hertz.

Dr. Perrone?

DR. PERRONE: Thank you. Jeanmarie Perrone. This is for the FDA, I think slide 4. I want to

clarify an entity. It's described here as, "in opioid-tolerant individuals, the absorption of naltrexone hydrochloride may increase the risk of precipitating withdrawal."

I think most people know that opioid withdrawal is often considered uncomfortable but not life-threatening like benzodiazepine withdrawal or alcohol withdrawal. However, there is a concept that when that opioid withdrawal occurs because of abstinence or non-access to an opioid that that is the more benign type of withdrawal.

When you have withdrawal that occurs as a result of exposure to an opioid antagonist like naloxone or naltrexone, you have something called precipitated withdrawal, which is not the same thing as precipitating withdrawal. But precipitated withdrawal can actually be a life-threatening entity, and we see a lot of this in patients who inadvertently are opioid dependent and buy suboxone on the street or other kinds of drugs that contain antagonists.

I'm just wondering if the warning

information is going to be spelled out in some way for the opioid users who may try to misuse this product and get into bigger trouble on the basis of that kind of mechanism.

DR. HERTZ: The notes from the discussion, like I still refer to my -- because the transcript is excellent, but it's long, and my notes typically capture the points that I need to rely on in particular or are interested in the short, so I was just taking notes, anyway.

I have to go back. I'll take another look at the proposed labeling to see where else we have that described. I know it's in there elsewhere, but I don't know if it's in there to the extent that it addresses your concern. I'll have to go back and take a look.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Hi. Thank you. I'm Michael Sprintz. I was just following up on what Dr. Winterstein was talking about in terms of the solvents, and you were asking for a clinical or a real-world scenario.

Essentially, what she's describing is you have someone who gets a script for 120 or 180 of these pills, and basically, they dump it into a solvent, give it a certain time period X of whatever that is, be patient. And then after evaporating or drying out the solvent, then you have a very large amount of oxycodone that can then be weighed, and cut, and split, and sold, and used.

So especially from a diversion standpoint, I could see that being pretty significant, meaning from a drug dealer perspective versus a drug user as well versus someone who's going to sit -- when we talk about an active addict who's starting to go into withdrawal, they're not going to wait however many minutes or hours it takes in order to do that.

But when you actually look at from a diversion standpoint and from a dealer standpoint, for them to dump a month's supply into a solvent, and dissolve it, and get the oxycodone out, there at least were four that she described. So that would be somewhat of a clinical scenario in which that would be significant.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Just a very quick comment without obviously being able to mention the solvent, if we look at MO-48, the three solvents -- and I have another question for the sponsor later -- the three solvents that were pointed out there, M21, 22, and 15 are very different than solvent M27 in terms of ingestibility and so on.

So that's in a sense the approach described, dissolving a large amount, and then getting rid of the solvent is an extra step of work that might not be necessary for these other three solvents, which are very similar to each other.

DR. BROWN: Are there any other questions? Dr. Fields?

DR. FIELDS: Yes. I was just going to respond to Dr. Perrone's question about withdrawal. There is a fairly large section in the warning section of the label that goes into a lot of detail about precipitated withdrawal and the severity of the symptoms, and it's in a couple of other places

in the label as well.

DR. PERRONE: Thank you.

DR. BROWN: Any other questions of clarification for the FDA?

Dr. Morrato?

DR. MORRATO: Since it got cut off before the break, I just thought I'd bring it up here. So does the FDA agree then with the statement that the fear of naltrexone is likely to limit extensive experimentation based on chatroom data? In terms of your overall assessment in the proposed labeling, it may be that that's what you agree to.

DR. HERTZ: I don't know that we would be able to clearly agree with that statement so that's a soft no.

DR. BROWN: Dr. Perrone.

DR. PERRONE: This is another question for the FDA. While we're discussing the concerns about 80 milligrams, I'm wondering if we have the opportunity to discuss the idea that if 80 milligrams of oxycodone in this drug is going to be given twice a day, that gets you to 160 milligrams,

which is definitely going to be far in excess of what our current recommended doses are of opioids.

So I realize that these studies were done prior to new guidelines recommending lower doses in general and less opioid use in general, but do we have an opportunity to, say, discuss this drug without including an 80-milligram dose?

DR. FIELDS: I think that might be a good thing to discuss when we get to the questions. That's a very good thing to bring up.

DR. BROWN: I hope you will please remember that and ask that question because it is something that should be brought to the fore.

Any other questions for the FDA before we go to lunch?

(No response.)

DR. BROWN: If not, we're going to break for lunch now. We are going to reconvene again in this room in one hour from now at 1:00 p.m. Please take any personal belongings you may want with you at this time.

Committee members, please remember that

there should be no discussion at the meeting during lunch with the press or any member of the audience. Thank you.

(Whereupon, at 12:00 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. BROWN: We're going to move ahead now with the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory hearing meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself?

(No response.)

DR. BROWN: Will speaker number 2 step up to the podium and introduce yourself.

MR. THOMPSON: Hello, and good afternoon. My name is Edwin Thompson. I am the president of PMRS, Incorporated, located in Horsham, Pennsylvania.

With great urgency, the opioid epidemic must be stopped and prevented from ever returning. The CDC guidelines for prescribing opioids for chronic pain published in March of this year highlights one of the primary root causes of this epidemic and the solution. The root cause is the availability of extended-release long-acting opioid products such as OxyContin. The solution presented in the CDC guideline is to significantly limit access to or if not eliminate the use of ER/LA opioid products.

The CDC has issued warnings about ER/LA opioid products in the past to no avail. How else do we explain the over $4 billion in sales in ER products and an increasing number of ER drug applications? Science and human concern would take you in the opposite direction.

It is reasonable that anyone submitting an ER opioid drug application believes the FDA is not going to implement the CDC guidelines. The CDC guidelines make 12 different recommendations that should be communicated, taught, and practiced by physicians and healthcare providers.

For this committee, I would like to focus your attention to the opioid drug recommendations. The guidelines are recommendations for primary care physicians prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. Your committees should aggressively consider adding these recommendations to opioid product labeling and should immediately include this information in all REMS programs.

The opioid drug recommendations start with the fourth recommendation. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of ER/LA opioids.

Here is why. No clinical evidence review of any approved ER/LA opioid has ever been found, has

provided evidence that continuous, time-scheduled use of ER/LA opioids are more effective or safer than intermittent use of immediate-release opioids. No evidence, no clinical evidence review of any approved ER/LA opioid has ever found that the use of ER/LA opioids reduces risk for opioid abuse or misuse and addiction.

Also, experts indicated that there was not enough evidence to determine the safety of using IR opioids for breakthrough pain when ER/LA opioids are used for chronic pain and that this practice might be associated with dose escalation.

Recommendation number 5, when opioids are started, clinicians should prescribe the lowest effective dosage. Effectively, this also eliminates ER products from starting chronic treatment.

Clinicians should reassess evidence of individual benefit and risk when considering increasing dosages to greater than or equal to 50 morphine milligram equivalents per day. Most experts agree that, in general, dosages to 50

morphine milligram equivalents per day increases overdose risk without necessarily adding benefit for pain control or function.

Again, this effectively eliminates the use of ER/LA products because most ER products are at the higher dosage strengths. For an example, this would eliminate the use of 20-, 30-, 40-, 60-, and 80-milligram OxyContin. Only 15-milligram dose BID and below would be acceptable.

Clinicians should carefully justify a decision to dose at greater than or equal to 90 morphine milligram equivalents per day. Still, this would eliminate 40, 60-, and 80-milligram OxyContin.

There must be restrictive labeling for high-dose strength opioid products. The guidelines reports on a recent study of patients 15 to 64 receiving opioids for chronic non-cancer pain and followed for 13 years. One in 550 died from opioid-related overdose at a median of 2.6 years from their first opioid prescription. Even worse, 1 in 32 who escalated to opioid dosage greater than

200 morphine milligram equivalents per day died from opioid-related overdose. This is 1 in 32 patients. An 80-milligram OxyContin is above 200 morphine milligram equivalents per day.

How could you recommend approval of a drug at this strength and not include this in the package insert?

Recommendation number 6, when opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed. This also eliminates ER products.

The guidelines also lists the following important findings. Patients who do not experience clinically meaningful pain relief early in treatment, for example, within one month, are unlikely to experience pain relief with longer term use.

Time-scheduled opioid use was associated with substantially higher average daily opioid dosage than as-needed opioid use in one study. No evidence shows a long-term benefit of opioids in

pain and function over no opioids for chronic pain with outcomes examined at at least one year.

When you list the CDC recommendations, the solution becomes very clear. When starting opioids for chronic pain, IR opioids should be used instead of ER/LA opioids. There is no evidence that ER/LA opioids are more effective or safer than intermittent use of IR opioids.

There is no evidence that ER/LA opioids reduce risk for misuse or addiction. There is insufficient evidence to determine safety of using IR opioids for breakthrough pain when ER/LA opioids are used. When opioids are started, clinicians should prescribe the lowest effective dose.

Number 6, increasing dosages over 50 morphine milligram equivalents per day increases risk without increasing benefit. This limits OxyContin to 15 milligrams BID and below.

Also, we know that compliance is not an issue. Patients in pain take their medication. The advantages of ER opioid products are patent protection, increased price, and dose escalation.

If the CDC recommendations were included in the review process of every opioid existing in new products and included in their labeling, you would make a significant step in stopping the opioid epidemic.

Critical to stopping the opioid epidemic is communicating the guidelines to clinicians and healthcare providers. The REMS program must be corrected. The blueprint must be rewritten. It must include the CDC guidelines and optimally as a part of product labeling.

Using Dr. Katzman's presentation and data from your last advisory committee meeting confirms this point. New Mexico mandated that all clinicians with prescriptive authority receive continuing medical education specific to chronic non-cancer pain. The result was that from 2008 to 2014, the number of drug overdose deaths remained the same.

This committee also removed the deaths due to heroin and adjustments for population, and the deaths remained the same.

Mandatory education was not successful. University professors teaching the course was not successful. Teaching the current product labeling was not successful.

I submit to you that you are teaching the wrong information. The CDC guidelines need to be added to the REMS program and to product labels.

Additionally, abuse-deterrent products should not raise price over generic products. Abuse-deterrent products do not cost more to manufacture and distribute than generic products. The research and development investment is miniscule and recovered in months. Patients should not pay tens of billions of dollars in price increases for abuse-deterrent products.

Abuse-deterrent labeling looks more like patent protection and profiteering than reduction in harm to patients.

Finally, an evidence-based review must be conducted for the approval and labeling for all existing opioid products and especially extended-release products before you recommend approval of

additional opioid products and prior to approval of abuse-deterrent labeling.

This advisory committee has the power to make a significant contribution to stopping the opioid epidemic by incorporating the recommendations from the CDC guideline in every opioid label. Restrict the prescription of high dose opioids as set forth in the guideline and allow their use only when the clinician can justify the use based on safety and efficacy. Include and teach the CDC guidelines in the REMS program.

Thank you.

DR. BROWN: Thank you, Mr. Thompson.

Will speaker number 3 step up to the podium and introduce yourself?

DR. WOLFE: I'm Sid Wolfe with the Public Citizen Health Research Group. I do not have any conflict of interest other than what the FDA might construe as an intellectual conflict of interest. I was on the Drug Safety and Risk Management Committee when it met on the topic of Embeda in 2008 and 2010. A lot of what I'm going to say

shows a, I think, deterioration of the standards then in place for thinking about abuse-deterrent labeling.

This is sort of an outline of what I'm going to talk about. The reason Embeda is there is because the same technology, as Pfizer agrees, was used in ALO-02 as was used in Embeda, and a lot can be learned, particularly how it took between 2009 when it was approved, and 2014 before any kind of abuse-deterrent labeling was allowed.

November 2008 was the first of these two meetings. I mentioned that I was there. I think Dr. Morrato was at the one in 2010 but not in the one in 2008. Yes. Okay.

There was a big mistake on this. This meeting was actually in 2008, November 11th. I confused those two numbers.

Alpharma whose drug it was then -- I just want to make clear Pfizer did not have the drug at this time, did not buy the company that had it until 2011. So what goes on in the next few slides is not Pfizer's doing at all, in all fairness.

The company said IV studies suggest selected naltrexone to morphine ratio is 1 to 25, no significant differences between whole and crushed. A lot of the same kinds of class I, II and III studies that the FDA has outlined were done on Embeda before its approval.

The FDA, on the other hand, looked at the same studies and said that, under selected conditions, morphine can be efficiency extracted in isolation from naltrexone from Embeda capsules. Once extracted, the morphine can be subject to abuse by various routes of administration.

After this, the drug was approved in 2009 with no abuse deterrence stated in the label, and shortly there afterwards, a couple months, the company was caught with a really misleading advertising campaign, promotional campaign. I'm mentioning it again; this was not Pfizer at the time, but it's the kind of thing that was done, even though there was no kind of labeling on abuse reduction.

These are some of the violations that they

left out from videos and so forth, that using it could result in a potentially fatal overdose of morphine, crushing or chewing. The other thing was failed to reveal that the co-ingestion of alcohol and Embeda may result in a potentially fatal overdose, fatal respiratory depression if you use it in an opioid naive patient, and a couple other things such as, under serious adverse reactions, they left out the fact that this could be using respiratory arrest, apnea, circulatory depression, everything.

Their overall conclusion was that the information in these videos and so forth grossly minimizes the serious potential risks associated with Embeda, and they misleadingly talked about abuse reduction even though there wasn't anything in the label. Remember, the standard for promotional materials is what is in the label, and we'll get back to that later.

We now jump forward to the meeting. Dr. Morrato and I were both there, October 21st, 2010, and you see a different flavor on what is

necessary for abuse-deterrent labeling. And I'm putting this up in this meeting because, at that meeting, they showed a slide saying that, in March 2005, there had been a pre-IND meeting to talk about postmarketing epidemiological studies. What you'll see is that the postmarketing epidemiological study will be submitted to the FDA in 2020 on Embeda, and then or later on any of these other drugs, if they get that.

This is a current schedule. As I said, Embeda did get abuse-deterrent labeling in 2014, and the study completion in 2019, and submitted to the FDA in 2020.

These are the things I was talking about in terms of the different attitude about the standard for abuse-deterrent labeling. We required demonstration in the premarketing program the kinds of things that you've heard about this morning that actually result in reduction of abuse and its outcomes, death, overdose and addiction, as confirmed in postmarketing epidemiological studies.

Then it appeared, and at that time, the FDA

was not giving any abuse-deterrent labeling -- that you needed to confirm the possibility of these studies that were done before approval really having any effect on abuse deterrence.

This is again quotes from FDA. These early studies, again, the first three, the extraction, the two abuse studies, might suggest how and to what extent a product purported to be abuse-deterrent may be manipulated and abused once the product is on the market. And then as opposed to suggestive evidence, the FDA is not used to approving things based on suggestive evidence. It should be actual evidence.

Particularly we're talking about abuse-deterrent labeling in this case. Only postmarketing epidemiological studies will reveal the extent to which a product purported to be abuse-deterrent will actually be manipulated and abused after it's on the market.

These are questions to our advisory committee, and the bold on top is the agency needs to provide a clear and consistent goal for the

company. This is in the context of what they are expected to do in terms of postmarketing epidemiological data.

The majority of the committee felt they would like to see the agency require both sponsors -- there were two different products up for them; one was, I think, another OxyContin product -- to specify the exact form of abuse or misuse that the product was designed to deter and then design epidemiological studies in a human population to look at that.

In March 1st, 2011, Pfizer bought what was then King, Alpharma's, I guess, derivative organization, and a week and a half afterwards, there was an Embeda recall due to naltrexone disintegration.

Dr. Hertz mentioned, I think correctly, that certain period of time between then and now, there wasn't much of it around because of the recall. Up until the time of the recall, though, there was well over 100,000 prescriptions filled a year, but since then, very, very little.

So the next thing we'll look at is abuse reduction now in the label. It happened in October 19, '14. And the completion dates again which I showed you before, I'll show in the context of this, though.

This is FDA's letter in October of '14 to the company saying the postmarketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Embeda, and I would say "if any" because it could increase. There are a number of ways that started getting discussed this morning in terms of extraction and so forth, where you could actually get more abuse rather than less abuse.

This is the actual label, and someone asked this morning, is it sort of similar to what was Embeda. And the answer is yes. The Embeda has properties that are expected, expected, to reduce abuse by the oral and intranasal routes. However, abuse of Embeda is still possible.

Then they talked about human abuse potential study afterwards, drug-liking, and so forth and so

on. You're not going to know that, the real abuse, as opposed to the possible until additional postmarketing data are available. Again, if this is approved and it's approved with abuse-deterrent labeling, it will be another four, five, six years before those are there. They also have to get ones on Embeda if they're going to leave it on the market. Again, to repeat that earlier slide, this is for Embeda, still a number of years to go.

Finally, or least semi-finally, the Wall Street promise, this is a quote from Pfizer back last year when FDA, I think, accepted the new drug application, and then data from the meeting, and some conclusions.

This is a quote from Pfizer's press release. "Abuse-deterrent opioid medications incorporate technology designed to make the product difficult to abuse yet, when used appropriately, provide patients with the intended pain relief."

Well, the idea behind it, no one could dispute that they're trying to do something like that, and the question is, does it actually deter

abuse? You can call something and label it as abuse deterrent, but you need to have evidence outside of a clinic. You need to have epidemiological evidence from a variety of sources which were discussed at this meeting in 2010 to show that it actually reduces abuse.

There's no doubt that, if it did, it would be an important step toward helping the drug to grow on, but they're already running up the flagpole, so to speak, that this is an abuse-deterrent opioid medication.

This we need to modify because of the correction that was made. I'll read the modification. The first one is exactly the same. The second one, "In conclusion, oxycodone is selectively extracted from intact ALO-02 pellets by a number of straightforward techniques."

Strike the last phrase because that's what the FDA said to do and instead, replace it, "Common solvents K through M are particularly effective in selectively extracting oxycodone from intact pellets."

The one phrase is wrong. These are again from the briefing package today, Pfizer's statements on ALO-02. You've heard some of this, but just it sounds like it's almost impossible to extract, release of oxycodone and naltrexone in 30 of 31 solvents studied. Similar and nearly complete release of both of them.

Questions were asked this morning, aren't there some solvents where it selectively increases? The FDA certainly thought so, which is what is in this slide.

Summary, after most physical chemical challenges, the formulation retained its abuse-deterrent features, and then finally, if the product is manipulated by crushing, naltrexone's released and acts as a common competitive opioid antagonist at the mu opioid receptor, resulting in reduce abuse potential.

They're already talking reduced abuse potential, no evidence for it. There's really no evidence for any of these abuse-deterrent preparations, that epidemiological evidence that

they actually reduce abuse.

Now, this is from, I think, Dr. Hertz's memo in the briefing package today, and there's a bit of, at least I believe, contradiction. You all may disagree. The first thing, a product has abuse-deterrent properties does not mean that there is no risk of abuse. I mean, how can one disagree with that?

It means rather that the risk of abuse is lower than it would be without such properties. Then on the same page of the briefing documents, "Sponsors with approved AD language in the label are required to conduct postmarketing epidemiological studies to determine whether properties of products result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction," whatever.

So on one hand, there's an assumption that simply using abuse-deterrent technology lowers the risk of abuse, and yet, out of the other corner of the mouth, it sounds as though meaningful reductions are not going to be able to be measured

until after the drug is on the market.

So Embeda was on the market for five years before they put the label on. When they put the label on, they had no more evidence of deterrence of abuse than is present now for ALO-02.

If you combine the misleading information again in the non-Pfizer promotional campaign in 2009 with this kind of tear between potential abuse-deterrent properties and actually reducing potential abuse, there's an interesting study published just two months ago by a group of people, one of whom is a fellow at the FDA now, Catherine Hwang. The others are Andrew Kolodny of Phoenix House and Caleb Alexander, who is actually on an FDA advisory committee.

They were asking a random sample of general practitioners, family practitioners, and internists around the country what they thought about attitudes regarding prescription opioid abuse and diversion, and this was to me the most striking finding. And it has to do with how misleading the concept of abuse-deterrent properties as opposed to

reducing abuse.

Of the people sampled, they got about a 58 percent response rate on a mail survey, 46 percent of them, almost half, thought that a drug that has ADF incorporated into it will have a lower addictive potential than a non-ADF of the same drug. There's no evidence for that whatsoever. It's theory. It's nice. It suggests, but again, suggests to me isn't strong enough to put something on a label.

Then 27 percent of them thought that ADFs of prescription opioids will result in large or moderate reductions of morbidity and mortality. That would be nice, but once you start advertising for them, because once you've got abuse deterrence in the label, you can advertise that it has abuse deterrence properties in it, you start increasing the use and certainly possibly increasing the abuse.

I think that a serious thought has to be given -- and I will go through these final conclusions -- the FDA industry guidance on abuse-

deterrent opioids evaluation and labeling, which was certainly applauded by all the companies making this, should be withdrawn and replaced with a regulation more favorable to patients than to opioid makers. It certainly will help in this "competitive market" to sell opioids, but in the absence of evidence that it actually reduces abuse, it's kind of iffy.

ALO-02 should not be approved because of serious concerns about increased risk. The increased risks were in the various forms that were described. Three out of four non-medical users of opioids get the stuff from their friends and family.

There's certainly the pill mills and that kind of stuff, but they get it, and they don't pay for it, and so forth. And if they're clever, they figure out various ways of getting more in a shorter period of time, and that increases the risk. And the abuse can also be increased very easily because the flip side of abuse reduction is abuse increase.

Easy manipulability, which was the question several people asked this morning, is clearly as easy for a variety of different solvents; can selectively extract oxycodone or to a lesser extent selectively extract naltrexone. But if you selectively extract the oxycodone, then you don't have to worry about the naltrexone.

Current labeling for opioids with potentially abuse-deterrent features as specified in the guidance, I think, should be repealed and replaced with a regulation as opposed to a guidance. It's too lax, literally encouraging companies to put in language that can easily be turned into promotional material, increasing, not decreasing use and abuse.

Just a couple comments since I have a little extra time. When I saw that Embeda got abuse-deterrent labeling in 2014, it was very upsetting because I was certainly aware of the history behind it, and it wasn't as though suddenly there were new data, epidemiological data on actual abuse deterrence in 2014. There was pretty much the same

data that were there when we looked at this drug in 2008 and it was approved without any abuse-deterrent labeling.

So I think the difference between abuse-deterrent labeling and not having it is something that the medical profession is very uninformed or misinformed about. Advertising promotion such as the campaign in 2009 certainly helped to foster that. I think that beyond the issue, but including the issue of this drug up for consideration today as the last speaker said, we not only include or incorporate the somewhat FDA-resisted CDC opioid guidelines, but think seriously about evidence.

We would never approve a drug as safe and effective unless there was evidence for it. We wouldn't do it just on the basis of it suggests that it's safe, it suggests that it's effect, and I think the standard for saying that it's a abuse-deterrent drug needs to be the same.

Thank you very much.

Clarifying Questions (continued)

DR. BROWN: The open public hearing portion

of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Before we do that, I have been asked to say that Ms. Chauhan has been watching the deliberations from the Green Room behind us, as it is more comfortable for her. So she is completely up to date on everything that we have done and prepared to make a determination about this issue with us.

The second thing that I would say is that the sponsor would like to clarify some points, so I'm going to ask them to clarify the points that they had in mind now. And then we'll give the committee a chance to go over some questions which we did not get to this morning.

DR. DONEVAN: Thank you, Dr. Brown.

So I wanted to come back to the issue related to the cut points because that certainly

came up during the FDA conversation as well as the discussion earlier with Pfizer.

If we could pull up MO-48, please, there was some discussion about this heat map in particular. So I thought it would be worthwhile to emphasize that we developed this for display purposes only as a way to communicate the data that we have in a way that's hopefully understandable to the audience.

The cut point of 0.5 specifically, which is the ratio of naltrexone to oxycodone, is just a cut point that we used. The brown shading represents in many ways that there is increase in oxycodone extraction, but in most cases, there's still naltrexone extraction, as I discussed before.

The cut point of 0.5 doesn't mean there's no naltrexone absent. It just means that there's less than the 0.5 ratio.

I also wanted to discuss the issue of time, which I think, Dr. Winterstein, you brought that up. To do that, I thought I would bring up Edward Cone who has experience not only with in vitro laboratory manipulation studies but also in his

former role at NIDA with prescription and drug abusers to provide some context of the timing in our studies and what an abuser is looking for.

I guess finally before we move to Dr. Cone is to remember that the time on this graph is not linear. You can't assume that just because one box is filled and the next one isn't, that that's a specific increment. It's an increment in time, but each increment isn't the same across the studies.

We described those in the closed forum, and hopefully, you can recall what the specific time points that correlated with each of those specific rows, which may be a little difficult.

DR. HERTZ: Right, but the time points can be discussed in this open session if people have specific questions concerning that.

I also just want to state that there was a question about the coding and how FDA's codes and the sponsor's code correlated. And I checked with Dr. Gerhard briefly about the ones he was particularly interested in, and I just want -- as we're discussing this, I have a little bit of

information.

The solvents for -- could you keep that slide up, please?

DR. DONEVAN: Sure. Could you pause that slide? Thank you.

DR. HERTZ: For 21, 22, and 15, they're fairly similar, but we did not code 21 or 22 because they were similar. We just coded common solvent K to M15. And then we coded common solvent O to M27.

So if there's any other cross-codings that come up, I'm looking at Dr. Gerhard. I guess he'll think about it a little more and let us know if there's any others he'd like us to check.

DR. DONEVAN: Can I just turn it over to Dr. Cone, and then we can have, if there's additional time for questions --

DR. WINTERSTEIN: Yes. If the times could be disclosed, I think, for the understanding of the committee, if that's possible to share, I think that would be helpful.

DR. DONEVAN: Well, we did share the

specific reference point, which was the black bar in the open session quite specifically, and I think Dr. Morrato recalls that point.

DR. HERTZ: Right. Again, I just want to state, for the company to hear again, this has been discussed at other open sessions. It is not considered company confidential. It's your choice what to say. I'm not going to force words out of you, but there's no reason based on our open and closed session requirements for that not to be disclosed.

DR. DONEVAN: Right. So the bolded line is one hour, for everyone's benefit, and then we can discuss some of the later time points as they come up.

DR. WINTERSTEIN: But what would be helpful is basically two boxes underneath that, basically where we have the common solvents 21, 22, and 15 hit the brown. And I understand that the brown, the green, all of this is arbitrary, but that seems to be --

DR. DONEVAN: Right. Yes. So give me a

second, and I'll come back. I'll let Dr. Cone discuss, and then I'll come back, and we can discuss those specific time points, okay?

But actually, after we turn it over to Dr. Cone, I'd then like Dr. Sellers to respond regarding naltrexone, and then there was some specific discussion regarding naltrexone as well. If we can go from Dr. Cone to Dr. Sellers, and then you can certainly come back and ask me additional questions.

DR. GERHARD: Just immediate clarification to FDA, are you sure it's K and not L?

DR. HERTZ: Let me get back to you.

DR. GERHARD: Thank you.

DR. HERTZ: We're sure.

DR. CONE: Good afternoon, everyone. My name is Edward Cone, and I'm a salaried employee of Pinney Associates. And Pinney Associates will be compensated by Pfizer for my time here and expenses.

Can we put the same slide back up? I know there's a lot of information on this slide, and we

thought it would be a reasonable summary. But I know there's a lot of confusion about the slide. I just wanted to make a few comments.

By way of background, as Sean said, I spent 26 years most of which I was head of the laboratory of chemistry and drug metabolism at National Institute on Drug Abuse. And for virtually all of those 26 years, I interacted with drug addicts on a daily basis and spent many, many hours talking to them about their practices.

After I retired, I went to work for Pinney Associates and have been involved in evaluation of abuse-deterrent products now for any number of companies for over the last decade. So I've seen a lot of abuse-deterrent products in a variety of formulations and technologies.

So let's go back to the slide. The time element there starts with the very top green row, and that's the earliest time point. And it's not a linear scale. The very bottom row is many, many hours of continuous extraction.

So in my experience with the drug addicts

that I worked with on a daily basis, they would describe their techniques, and there's also published literature about people who tamper and manipulate various pharmaceuticals. There's a general consensus that they'll spend upwards -- they'd like to spend a minute or two because they want their dose, but upwards they'll spend enough effort over a span of 10 or 15 minutes. And that's the majority of people who try to manipulate these products.

Now, that span of 10 or 15 minutes is represented by the top one, two, three, and maybe four rows across. Now, if you put an IR product in a solvent, it's going to come out almost completely in that first row of two or three green boxes. And for selected solvents, all controlled-release, extended-release opioids, if you extract them with the right solvent, they will fully be released on that bottom row.

So that's kind of the two levels as a perspective. IR, if you want to call it failure in this context, the drug is actually doing what it's

supposed to be doing. It's delivering drug. The IRs are going to deliver drug in those first few green boxes, and the extended release is going to always deliver drug in that lower box.

Because of the guidance that says make your product fail, I'm paraphrasing, but it says take it to failure. So when we design these types of studies, that's literally what we do. We try to the best of our chemistry knowledge to fail these products, and the manufacturers don't always like that. That's kind of counterintuitive, but as chemists we know how to pick solvents that has the best chance of making them fail.

Now, in the context of ALO-02, we're dealing with two very similar molecules chemically, oxycodone and naltrexone. And it's a real challenge to separate those two compounds because of their chemical similarity. We found a few that would, but very few and only at specific time points and specific conditions.

So for a few of those solvents, the drug is doing what it's supposed to do when you see these

brown boxes on the bottom. The drug is coming out. That's what it's supposed to do. But for a few of those others, we found some selective time points with exotic solvents, and most drug tamperers don't use exotic solvents.

We threw a lot of really toxic solvents. Most drug users won't use those toxic solvents. They don't know what to do with them once you get it out in a toxic solvent. There's a few people that know what to do with it, but by and large, it's the really basic solvents that are the effective ones to ultimately release a controlled-release drug.

For most of those, though, just one more clarifying point, the brown box in most of those solvents does not mean oxycodone only. It just means it didn't reach this arbitrary cut point that they're using to suggest the ratio is higher in this case and lower naltrexone content in this case. So you can't look at those boxes as failures, but rather it's just a little bit more selective extraction.

With that, I think the essence of it is the presence of naltrexone is almost any concentration that's above a few tenths of a milligram is going to have an impact on the drug abuser. With that, I'll turn it back over to Sean.

DR. DONEVAN: Actually, if we could have Dr. Sellers come up, please, thank you.

DR. BROWN: If we could, move ahead with this.

DR. DONEVAN: Yes.

DR. SELLERS: Good afternoon. My name is Ed Sellers. I'm a professor emeritus of pharmacology toxicology, medicine, and psychiatry at the University of Toronto. I'm here as an independent consultant to Pfizer. I have sat on numerous scientific advisory boards, including for Pfizer, and I do chair the scientific advisory panel for opiate analgesic abuse for Health Canada.

I have no financial interest in Pfizer, or in this product, or in the outcome of this particular meeting. My travel here, the company that I use as a consulting company will be

reimbursed, and they'll receive an honorarium for my attendance here.

I want to put in perspective some of those brown boxes and get back to the question asked by Dr. Morrato about the cut point and its sensitivity. As Dr. Cone indicated, that was a somewhat arbitrarily selected cut point, and I think as Dr. Morrato was trying to get at, the definition might make quite a difference to how many brown boxes there might be. And this then relates to what do drug abusers think about the product that might have an antagonist in it.

To put this in perspective, I worked for 40 years as a clinical psychopharmacologist in research, in clinical care, and teaching. We've published extensively, and our work is highly cited. I've been PI on at least 100 abuse-potential and abuse-deterrent type studies.

A lot of the methodology that our group developed is actually incorporated in the guidances that are relevant to this. We either developed the methodology or refined things that already had

existed.

So if I could have slide CP-15, the cut point of 0.5 strikes me as being fairly arbitrary, and what I've put up here are some data that might suggest that lower cut points might be relevant to this issue of the drug of antagonism that you see by naltrexone. Naltrexone is a very potent antagonist. In technical terms, it has a Ki which is actually much lower than the binding that you see with, for example, morphine and oxycodone.

So these are the data from the Pfizer studies for their human abuse potential studies. This shows the intravenous, intranasal, and oral studies. In those studies, as you'll recall, the intravenous and intranasal study showed huge reductions. I say huge based on my experience. These are very, very big effects of the naltrexone on decreasing the Emax compared to the oxycodone comparator.

In those studies, it was possible to look at the ratio of naltrexone and oxycodone, and as you can see for the intravenous and intranasal, this

was actually about 8 or 9 or 10 percent. This would suggest that ratios of the antagonist to the agonist much, much lower than 0.5 would give rise to substantial antagonism of the opiate effects. In fact, the oral study suggests that ratios that are down in the order of a few percent would be having an effect that would be clinically important.

So the issue, as I see it, is those brown boxes. As Dr. Donevan suggested, this doesn't mean there's no naltrexone. The issue of lower cut points -- my guess is that a lot of those brown boxes are going to show that there is sufficient naltrexone present to have a substantial degree of antagonism.

Now, the second thing I want to address is the question that came up about would having naltrexone in there be perceived by abusers as being a bad thing and they might avoid it. If I could have KOL-8.

I'm aware of at least three published studies; well, two published and one presented that

look at what drug abusers say about antagonist-containing products. Now, this is one study that we did in a group of drug abusers who tamper. And we gave them examples of a number of real and hypothetical products, and then we asked them using a number of previously used and validated scales, things like opiate attractiveness, and value of the product, and how much they would pay, and their likelihood of tampering with it.

Across the board, the product that at the time was hypothetical was oxycodone and naltrexone was always at the bottom of the list, and this is consistent with the other publications. It was previously mentioned in chat rooms that you see talk by abusers that they don't like antagonists, and from my experience clinically, that's exactly the case. In my clinical work, I had lots of contact with opiate-dependent individuals.

Now, of course, the internet makes -- there can hardly be an abuser out there that is not aware of narcotic antagonist pharmacology and what it can do. You go to Bluelight or some of those other

sites, you'll see warnings about products, well, like Embeda. That's the kind of comment you see.

Now, this is a little bit anecdotal. From my experience, it's entirely consistent, and the final thing I would say --

DR. BROWN: Excuse me. Could I get you guys to wrap it up, please?

DR. SELLERS: I'm sorry? Yes, absolutely. Just as I said, final comment would be that I've done studies in individuals who are opiate dependent, methadone dependent, for example, and they are exquisitely sensitive to intravenous antagonists like naloxone, doses of 0.1 or 0.2 milligrams.

So this kind of pharmacology coupled with what the abusers think of an antagonist make me pretty confident that just the presence of the naltrexone as well as the pharmacology will make this a robustly abuse-deterrent product.

DR. BROWN: Thank you for those clarifications.

We're going to move on now to ask you some

specific questions, and we're going to go to Dr. Gerhard first.

DR. GERHARD: Tobias Gerhard, Rutgers. Well, let's stay with the infamous slide MO-48 to start with --

DR. DONEVAN: MO-48.

DR. GERHARD: -- hopefully, a clarifying question.

DR. DONEVAN: Yes.

DR. GERHARD: Could we get the slide up?

DR. DONEVAN: Yes.

DR. GERHARD: So I think this will address all the issues that came up with time and how much naltrexone is released, when. Do you have the extraction profile that you show for solvent MO8 and M16? Do you have that for either M21, 22, or 15? How much release over time oxycodone versus naltrexone? Is the naltrexone coming out in 21, 22, and 15, or does it look like MO8, just in a different time?

DR. DONEVAN: You're asking M21 -- let me just look at the -- M21, does it look like product

MO8? No, it doesn't look like product MO8 exactly. I don't have the profile with me right now.

One thing I can tell you is the time for the bar, okay? If we take M21, for instance, the first brown shading is at three hours. Okay? And at that point, we begin to see oxycodone extraction in the absence of naltrexone.

DR. GERHARD: Well, the FDA information says 90 percent is extracted.

DR. DONEVAN: They actually corrected, I believe, their statement and said that at six hours, there was 90 percent extraction of oxycodone.

DR. GERHARD: Okay. But how much naltrexone at that time point?

DR. DONEVAN: At that time point, there was greater than 30. I don't have the numbers right in front of me, but it was greater than 30 percent extraction.

DR. GERHARD: So that doesn't separate.

Then a question to MO-21.

DR. DONEVAN: MO-21.

DR. GERHARD: It might be for Dr. Wolfram.

DR. DONEVAN: Slide MO-21, you mean?

DR. GERHARD: Yes. Sorry.

DR. DONEVAN: Great.

DR. GERHARD: This is the single-arm long-term effectiveness study. Do you have the average daily doses over time? You show that the average daily dose over the entire study is 62.5 milligrams per day, but how much up-titration was there? Did you look at that? Do you have those data?

DR. DONEVAN: Yes, we have looked at that. Just to remind you, this is study 1001, which is an open-label study.

Dr. Wolfram, would you like to come up, please?

DR. WOLFRAM: Sure. So may I have slide number EF-45 on the screen, please?

What you can see here is, at the visit, the concentration, the average dose is in milligrams, and you may remember that there was a four-week titration period. And the patients were coming in with pain scores of around 6, and in a matter of

four weeks, pain decreased significantly to a level of around 4 and stayed at that level throughout the 12-week period.

What you can see here is that the doses gradually increased. There was a taper period involved, and from months 2 to 3 on, the doses slightly increased. From month 6, you see on the bottom on the average doses in this little table of around 71 -- these are average doses in milligrams -- stayed constant over the rest of the time.

DR. GERHARD: Yes. But still over the course of the study, they double, and they certainly at the end exceed the average of 62 by a significant margin.

DR. WOLFRAM: Yes. I may add here that this is observed data, so this means there are the patients dropping out at the end, of course, for a reason, for insufficient pain relief or for whatever reason in the end. They tend to increase the doses in the end.

So these time points are not imputed data,

so this is observed data.

DR. GERHARD: So the Ns aren't the same for each time point. They get smaller over time?

DR. WOLFRAM: Yes, correct.

DR. GERHARD: So in other words, if everybody had been treated at even -- the people who dropped out may have even required higher doses than this?

DR. WOLFRAM: Exactly, yes.

DR. GERHARD: Thank you. And dose per day or BID? I assumed that it was daily dose, but yes.

DR. WOLFRAM: Yes. So in that particular study, patients were allowed to start the titration with the once-daily 10-milligram dose, and then proceed to 10-milligram BID, and stay on a BID dosing throughout the study on whichever dose they were at the stable level.

DR. GERHARD: Any number of --

DR. WOLFRAM: Daily, yes. So these are daily doses BID.

DR. GERHARD: Thank you.

One last question to slide MO-62?

DR. DONEVAN: MO-62, please, thanks.

DR. GERHARD: This is for the question of taking the drug again. To me, there is a surprising difference in just taking without any extraction the crushed oral form comparing to oxycodone IR, either the 40-milligram or the 60-milligram. One question would be, why not 80?

The other, is there any explanation that you could come up for this difference because the whole argument of the product is that the ratio of naltrexone is responsible for the effect of the abuse deterrence. The ratio stays the same, but for the smaller dose, the scale score is 56.5. For the 60-milligram, it goes up to 71, although the ratio stays constant. We obviously don't know if you don't have the data what happens at 80.

DR. DONEVAN: We didn't explore a higher dose in this study. We did discuss the study with the FDA, and in those discussions with the FDA, selected these doses which are common doses used in other abuse-deterrent studies with oxycodone.

Dr. Sellers, would you like to respond

regarding the significance of the data?

DR. SELLERS: Yes. The reason these studies don't use higher doses is primarily a safety issue. The fact there's no dose response apparent here with 40 and 60 is largely because of the subject selection criteria. These are recreational drug users who go through a qualifying session where they're given 40 milligrams of oxycodone. And they have to be able to tolerate it and also report drug-liking.

We very frequently see that with this group of individuals who can tolerate 40 milligrams, it doesn't mean by giving them more that they're necessarily going to get more liking or whatever. The side effects start to become evident, and this is one of the reasons why you see on the drug-liking score and here with the take drug again that it's likely in this study that what you're getting with higher doses is actually a little bit of some of the adverse effects of the opiate.

So you get this plateau of effect. If you gave 80, my guess is that you'll see antagonism of

some of the effects, but you'll also probably see a score that's lower than what you have for the 60 because of the more adverse effects. It won't be dose escalation.

DR. GERHARD: But that's not what the data shows. The data shows that the likelihood of taking the drug, wanting to take the drug again is increasing. That it might be plateauing at higher doses is completely not borne out in the data. That's something that might be true, but we don't know.

DR. BROWN: Dr. Sellers, what Dr. Gerhard is saying is that, based on the linear data that we have here, unless you have some scientific basis for helping us to understand why there shouldn't be a lower take drug again for 80 milligrams, that would be what we would presume would happen.

DR. SELLERS: I would expect, in this group of recreational non-dependent users that with 80 milligrams, you would see lesser desire to take drug again.

DR. BROWN: I guess I don't understand that,

but maybe we can move on.

DR. SELLERS: For oxycodone on its own, yes.

DR. BROWN: Yes. No, we're talking about ALO-02 60 versus oxycodone IR. We're talking about going to 80 with 80.

DR. SELLERS: It is possible, obviously. I mean, the product with higher doses, you will get more opiate exposure, but compared to the IR, the amount of increase will be less. So you're right, you might with the AL see an increase. It might. But if the question is around will this lead to dose escalation, it doesn't follow from this kind of study that that would be the behavior.

DR. BROWN: Okay. We're going to move.

DR. DONEVAN: I guess the only other comment I would like to make is that the study was actually powered for the two primary endpoints, which were drug-liking and high and not for this specific endpoint.

DR. BROWN: Dr. Gupta?

DR. GUPTA: I had a question again, I'm sorry, about the solvents. I was just wondering,

the solvents in question that we're all discussing on MO-48 specifically on slide MO-48, MO-44, both of those slides, the graphs that you have inset in there; is there a possibility to have them -- can we look at them in a closer detail?

DR. DONEVAN: So we have M27 that we can show you. If I can see -- I've just got to find it, which slide it is.

We have this both for intact as well as crushed ALO-02. Could we go to the crushed ALO-02 which is -- hang on one second because the title says the same thing for both slides.

The first slide I'll show you is slide AH-2, if we can pull that up on the screen, please.

This is solvent M27. It says "intact pellets," but it's actually crushed pellets. This is crushed pellet data. For a reference point, the timeline goes from on the X axis from zero to 4 hours. That gives you the time.

You can see that even as early as at the first extract, you see roughly 30 percent extraction of oxycodone and approximately between 5

and 10 percent extraction of naltrexone. And as time goes by, you see an increase in both oxycodone extraction as well as naltrexone extraction.

DR. GUPTA: Can I just make sure I'm understanding this correctly so that I can clarify in my mind?

DR. DONEVAN: Yes.

DR. GUPTA: This graph is basically demonstrating that at 4 hours approximately, between 60 to 80 percent, somewhere in there because I can't see the endpoint --

DR. DONEVAN: Yes, at 4 hours.

DR. GUPTA: -- of oxycodone is released and about 20 plus percentage of naltrexone is released under this particular intact solvent M27?

DR. DONEVAN: Yes. This is solvent M27 with crushed pellets. It says "intact," but it's crushed.

DR. GUPTA: It's actually crushed. All right. Thank you. That's all. I wasn't clear.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Yes. I actually had a

question back to MO-18, and I was just kind of curious because in the 12-week double-blind placebo-controlled study where the patients were screened and it had four to 6 weeks of an open label of ALO-02 and then they went on to either having double-blinded with ALO-02 or a placebo. I guess if you -- when we look at -- I guess go to, yes, MO-18.

Then when you look at it, I do understand that the numbers were based off of taking it from randomization to the end of study.

DR. DONEVAN: Yes.

DR. SPRINTZ: But if you actually look at the screening, they went from an average pain score of 7.1 to an end of study at 4.3 with the placebo. I thought that was kind of interesting. I didn't know if you had any information on what you attribute that to.

They were placed on ALO-02 for four to six weeks and then were actually taken off of it, but their pain score at the end was actually pretty significantly decreased from where they were at

screening.

DR. DONEVAN: Yes. I guess first to reiterate, that we did see treatment effect, so there was a separation between placebo and ALO-02 at the end of the double-blind treatment period. What we saw with placebo was that there was less return to their previous pain scores, which you identify.

What I'd like to do is pull up Dr. Rauck, who is an experienced pain physician, and has participated in our study, and can describe, and can comment further.

DR. RAUCK: Hello. Richard Rauck, Wake Forest University and Carolina's Pain Institute. I'm a paid independent consultant to Pfizer on this. I was also an investigator on both the 02 and 01 trial and also in many of the other opioid trials of this nature.

So it is a feature of enrolled in rich randomized withdrawal design. In fact, if I can have slide EF-27, it may show a little more of what you're taking about and the nature of this.

As you see, I think the effect of opioids and at least the efficacy of opioids are demonstrated here in the open label part where they do, as you noted, go from 7 down to really 3 at the randomization. Those are all patients getting opioid.

It's been an interesting phenomenon in these trials. In almost all of them, if you look at these, that as you noted, the placebo patients don't go back to baseline. I think there's been some interesting work by Irene Tracey, who does a lot of fMRI stuff as well that if you look in brain imaging and fMRI and look at analgesic areas that we know light up, when they're on placebo in these trials, the same analgesic areas light up.

Now, if you tell a patient he's on placebo, it seems like that effect goes away. So it seems like a unique characteristic of the experimental design in analgesic trials in particular.

So they do separate from placebo. I think you see again in the early phase the effect of the drug because they all get the drug at that point,

right? They do have profound analgesia there, and they do sustain the effect on drug over 12 weeks, which is encouraging.

But you are correct that the placebo groups don't rebound in these 12-week trials that way.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: This is good timing, actually, because I was going to ask about the missing data in your clinical trials. The briefing documents touch briefly on the issue of missing data, and you said you've done five sensitivity analyses and that three of them, they all continued to favor the drug and three of them were statistically significant. But they were varying degrees of what I would consider to be acceptable analysis data for missing data.

So I was hoping you could comment some more about that.

DR. DONEVAN: Yes. With that, I'll call Dr. Wolfram up to the stand, please.

DR. WOLFRAM: May I have slide EF-7?

So here, you see the sensitivity analysis we

performed. The primary analysis, that's what you saw in the previous slide, which is in the main open document. And you see here the treatment difference between 0.62, and then you see different methods of imputation. For example, a complete case or pattern mixture model, single-imputation method, mixed-model, repeated measures, and screening observation carried forward only.

If you look here, you can see that these five additional analyses all shot into the same direction, that treatment difference was favorable and compared in the same direction as the primary analysis. In fact, three of those analyses were highly significant.

DR. BROWN: Dr. Winterstein?

DR. SHOBEN: Do you --

DR. BROWN: Sorry, sorry.

DR. SHOBEN: Can I -- do you have information on the number of patients that were both at the end of your 12-week study and at the end of the 12-month study? So those graphs, it was MO-21 for the open-label 12 months' study. We were

talking about it briefly with Dr. Gerhard's question in terms of how many patients were actually still on drug at that time. Do you have that information available?

DR. WOLFRAM: So this is what you saw with the sensitivity analysis. This was the 12-week trial --

DR. SHOBEN: Right, I understand that.

DR. WOLFRAM: -- the controlled 12-week trial. And for the 12-month trial, I cannot show this data right now. And I think we did not impute the missing data.

What we do have is we have completer data, if you're interested in that.

DR. SHOBEN: Yes.

DR. WOLFRAM: If I can show the completer data slide EF-47, actually, what you can see here is the doses over time in patients who completed.

This shows you that basically the same observed data in general we saw up to month six, that the dose is lightly increased and then stayed more or less on 75 to 76 milligrams per day.

DR. SHOBEN: Right. But what percentage of patients who started the trial were still on the study drug at, say, six months?

DR. WOLFRAM: If I can have slide EF-15, you see the disposition of patients here, and what you can see here of the total enrolled patients, discontinued patients, so we split it into opioid-naive and opioid-experienced patients. But around 60 percent discontinued, and you see completers around 37 to 40 percent.

DR. SHOBEN: Thank you.

DR. WOLFRAM: Would this answer your question?

DR. SHOBEN: More or less, yes. Thank you.

DR. BROWN: Dr. Winterstein?

DR. WINTERSTEIN: At the risk of beating a dead horse, I think we're still somehow trying to get our arm around how much of a separation there is in the extraction and then also how much the naltrexone really affects the liking.

I heard two major comments with respect to MO-48. One was these are mainly toxic solvents. I

know that we cannot talk about the toxic solvents, but the three ones have one thing in common and that is, they are not toxic and they are commonly available.

DR. DONEVAN: Right. Yes.

DR. WINTERSTEIN: So that's, I think, one very important consideration in thinking about how likely it would be for an abuser to wait three hours and get something nice out of it.

DR. DONEVAN: So that's true. I guess, just in going back to Dr. Cone's comment regarding time factor, so at the earliest time point where there's at least 30 percent extraction, that's three hours after extraction. And as Dr. Cone indicated, typically, abusers like to get their drug extracted much earlier than that.

DR. WINTERSTEIN: But it wouldn't be too much trouble to get that particular solvent and digest it. And if there were a plan, that would certainly be not so hard.

Then the other part is this slide again, that MO-62 slide that Dr. Gerhard brought up, where

there was a little bit of a misunderstanding how to interpret the effect. Maybe we can look at this one more time.

DR. DONEVAN: MO-62, please.

DR. WINTERSTEIN: But I think that's MO-62, yes. I think that the comment about that these type of subjects may not really appreciate a higher dose explains why the brown bars pretty much stay the same, right? That basically means you give them higher doses and you don't get more liking out of this anymore.

I think what Dr. Gerhard was referring to, that the blue versus the brown catches up, and that is a very important observation. So when we're looking at the 40-milligram dose, there's clearly strong separation, but when you're looking at the 60-milligram dose between the comparison of ALO-02 versus oxycodone IR, this is catching up. And this is catching up quite significantly.

Since there is -- it's 0.7, so we are -- there's borderline statistical significance, and, to me, I don't know how I would interpret a liking

of 70-something percent versus 80-something percent. But there's not that clear separation anymore.

What that means is, since we still have the same ratio, as Dr. Gerhard already alluded to, of the naloxone, the naloxone doesn't really seem to combat that so much anymore. Now if we're thinking about this, in those extraction studies, the same thing would apply here. So the more I can reduce the naloxone and increase my oxycodone, I might get more effect out of it as well.

I think that's, to me, the major issue that we're dealing with here. Does that make sense?

DR. DONEVAN: I guess, if I can comment, I think you have to consider our abuse potential data in terms of the totality of the evidence. If I could show slide MO-60, please.

This is the drug-liking data for the oral abuse-potential study, and you can see that we got clear and significant differences at both 40 milligrams as well as 60 milligrams. This was the drug-liking data where we saw roughly a 16-point

treatment difference.

If we go to the drug high data, MO-61, thank you. We saw similar treatment differences between the IR oxycodone and the corresponding crushed ALO-02.

In the context of all the data, there seems to be a significant difference both at the 40-milligram dose as well as the 60-milligram dose. And I think it would be important for Dr. Sellers, if he could come up, to at least describe the meaningfulness of the differences that we're seeing in these oral abuse-potential studies.

DR. SELLERS: I didn't answer the previous question very well at all. And this is probably not the forum to debate whether the overall drug-liking or the Emax of drug-liking at a point in time are the best measures.

What I can tell you is that the overall drug-liking or take drug again measures are done at typically 12 and 24 hours. So they require a recollection of what is that's gone on, and usually, as one of these somewhat boring study

sessions goes on, individuals get tired. They start to have some opiate side effects.

What we see with the take drug again measure is that the absolute values tend to be less than you see with the high or the drug-liking simply because it's a synthesis of what they've experienced. And the other thing we see is that the variance on the responses are higher.

So I think that what is going on here is that the measure, which is appropriate to focus on because it's got face validity, sounds like it makes sense. I think it's just got more variance. It's occurring later in time. Recollections are not entirely as accurate as a moment-by-moment.

I think that the kind of way of looking at it is look at the drug-liking, look at the high, look at overall drug-liking, look at take drug again and all the other measures which haven't been presented here, but they all appear to be convergent. And worst case, by chance, you might have ended up with the result on the take drug again not being significant.

DR. BROWN: Thank you, Dr. Sellers.

We're going to move on now to Dr. Hertz giving us the charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: I know it's getting late in the day, and many of you have been in that same spot for two days. The good news is you're somewhat familiar with what we're about to ask you in a sense because it parallels a lot of what was done yesterday.

Thank you for your time and consideration, being here today.

As you think about these questions, in particular, we're going to ask you specifically whether you think there are properties that can be expected to deter abuse by the three routes identified. We're going to ask if you think that the product should be approved for the indication and, if approved, if it should have labeling.

I'd like you to keep in mind that we have regulations that describe the conditions for which we approve and not approve a product. There are

very specific deficiencies in an application that support a decision to not approve. We don't have a condition under the current regulations about a reason to approve related to not being better than what's already on the market.

That's often challenging because I know that a lot of people are interested in furthering the safety of our products. So as you think about the reasons for your decision regarding approval or not approval, please try to make sure that we have an understanding of how you've decided to support your vote, and we find that discussion as important as the actual vote themselves.

So once again, thank you for your time, and I look forward to hearing the remaining discussion and voting.

Questions to the Committee and Discussion

DR. BROWN: Thank you, Dr. Hertz.

We'll now proceed with the questions to the committee and the panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees

may not participate except at the specific request of the panel.

We can put the first discussion question on, which I'll read. "Please discuss whether there are sufficient data to support a finding that Troxyca ER oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse."

As you make your comments, I'm going to ask that you comment on all three of these routes of abuse.

Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. So I think the issue is really whether the two agents basically can be separated and how much effort it is. So obviously, we didn't discuss the specifics, and it would be a lot of work for anybody to figure out what the optimal conditions are, but in a sense, unfortunately, in a time of the internet, if there are ways to do it, this will come out.

I think the question is not that you'd have to try 40 different approaches, if it's doable, it will come out. So the question then is how cumbersome is it, and obviously, the product has to come out. Otherwise, it wouldn't be a drug suitable to treat patients.

The problem here is that although it might take with some of the conditions that work, that succeed in getting that separation of naltrexone from the oxycodone, that it might take a long time but that the effort required to do it is minimal and that the solvents or equipment used is minimal. It's cheap, readily available. It takes some time, but it's easily doable.

For some of the solvents, the ones that take very long, I know it's not an exceeding amount of time, but at the bottom of this slide that we saw, so, for example, the number 8, that we have seen that it completely separates them. No naltrexone is extracted, only oxycodone.

For some of the others, we really didn't see the data, so I'm happy to kind of take the

sponsor's word for it, but I didn't see data for the three solvents discussed. There's one more that's also similar that's somewhere in between. I didn't see the data so I'm somewhat concerned.

I think at the end of the day, if there's a way with low effort even if it takes some time to extract selectively the oxycodone, then we really have a problem, and that, in my mind, seems to be the case. And that certainly affects the oral route.

For the other two routes, it seems that the whole idea of this product is that when crushed, the two components don't separate. So I think, for the nasal and intravenous routes, there is somewhat more evidence, but again, the primary route of abuse is oral, so I'm not sure whether one could give selectively only abuse-deterrent for nasal and intravenous if the oral route isn't met. I'm not sure whether that's the intent of FDA or whether that makes any sense.

DR. BROWN: Dr. Emala? Could you state your name, please, sir?

DR. EMALA: Charles Emala, I want to slightly disagree in the sense that in the bottom column where the brown boxes appear does not mean there's no naltrexone. It just means that the cutoff points of the ratio and the total extracted oxycodone has been achieved.

Furthermore, in general, I think from the tone of the discussion, the cutoff points are rather conservative in the sense that that doesn't mean because there's a brown box there's no protection. And I'm also encouraged by several of the ingestible solvents, which actually with time extract an increasing amount of naltrexone, suggesting that you'd have to find that magic window in those particular ingestible solvents.

So I think it's important not to misinterpret the brown boxes as meaning that there's all, or nothing, or no protection. It's just that the arbitrary cutoffs of greater than 30 and a ratio of greater than 0.1 has been exceeded, but we don't have evidence that that doesn't mean there's still some deterrent potential.

I think in the overall incremental advancement in abuse-deterrent formulation, I think there's evidence here for oral abuse deterrence. For both nasal and intravenous, I actually am pleasantly surprised to see visual analog scales that changed 20 to 30 points. I think some of those measurements of clinical drug-liking and so forth is quite impressive. I think there's evidence for potential deterrence for all three categories.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Just immediate response, I completely agree that the brown box doesn't indicate that no naltrexone is extracted, but in the case of, let's say, solvent MO8 on slide MO-48, it specifically shows the extraction profile over time, and it shows no extraction of naltrexone at any time point, if we can pull up slide MO-48.

That's basically the condition that's somewhat similar to what happens in the digestive tract where there is no naltrexone dissolved because otherwise, the drug wouldn't work. So

that's inherent in having the drug working, but that doesn't mean that it's not also causing a problem.

In contrast, when looking at the profile for M27, that's only on slide MO-45, there, I agree. You see an extraction of -- so here, for solvent MO8, you see no extraction of naltrexone even after the entire timeline is extended.

So that's, I think, the problem in contrast, slide MO-45. There, for solvent M27, that's exactly what you described. There is extraction of oxycodone, but there's also extraction of naltrexone that's under 50 percent. But that cutoff might not be -- and I agree, that cutoff isn't necessarily the end-all here and the smaller proportion might be sufficient.

But if it can really readily be completely separated, then we have a problem.

DR. EMALA: If I could just respond to that, I think you're referring specifically to MO8, showing lack of --

DR. GERHARD: MO8 is the only one where we

saw the data.

DR. EMALA: Right, and MO8, if you look at the brown box --

DR. GERHARD: Not MO8 crushed here, but MO8 in the complete pill because the crushing, obviously, is the intention of the product, so here in, yes, MO8.

DR. EMALA: Right. So in both cases, on this intact pellet for MO8, there's no naltrexone extracted whatsoever, but if you look at the time point for when greater than 30 percent of oxycodone occurs, it's at the very longest time point.

DR. GERHARD: Exactly, and we haven't really seen it for M21, M22 or M15, and particularly also for M14 which is somewhere in between the two, and that will, I think, determine since I haven't -- I would like to see the data to be sure that there isn't true separation, and I haven't unfortunately.

If the situation is like for these solvents M28 to M26 on the right-hand side, that's very difficult to achieve in practice. If you have a window of 20 minutes where enough oxycodone is

extracted to make sense, but you don't have the naltrexone, then it comes later, that's something that I think we wouldn't have to worry about it.

But if there is -- even if it takes some time away to just safely extract the oxycodone without getting naltrexone, then I think, even if it takes some time, if it doesn't require effort, I think it's a problematic situation that might very much lead to abuse in practice.

DR. BROWN: But, Dr. Gerhard, would you not agree that under 95 plus percent of every scenario that's been presented to us, given the fact that these are conservative estimates of the relationship between oxycodone and naltrexone, that the abuse-deterrent properties are held?

DR. GERHARD: But if no naltrexone is extracted, if I can just throw it in a bottle of solvent X -- and solvent X is something that I can buy at the supermarket, and take home, and drink right now. If I can just take 10 pills, throw it in a bottle, let it stand for two days, what I have then is a solution of oxycodone without extracting

naltrexone, and they just filter the remains out. That takes two minutes of active effort, and I get everything I want in a refreshing drink, then I have a problem.

I haven't seen anything that convinces me that that's not possible here.

DR. EMALA: Can I just follow? I think we can agree there's no perfect irresistible formulation for the solvents. The question where you draw the line is some level of deterrence.

DR. GERHARD: Exactly. But I think, in terms of time commitment, the important thing is spending two hours in grinding something, that's a lot of effort. Spending 30 seconds of throwing a pill into something and then waiting two hours is very different from that, although they both take two hours of time or 12 hours of time.

But without active work and with readily available and cheap ingredients, I can create a solution that is readily consumable. That's problematic. It's not the fault of the product. It has to happen because that's what happens in the

digestive tract, but it's still a problem.

DR. DONEVAN: So can I comment? I don't know if I'm out of place here commenting, Dr. Hertz.

DR. HERTZ: I really think we need to reserve the time for the discussion unless there's another clarifying question raised.

DR. BROWN: Dr. Morrato?

DR. MORRATO: I appreciate both perspectives here, and I think maybe in hindsight, showing the heat graph raises more questions and concerns, then maybe leads us down different pathways.

But I am troubled, though, by FDA's own conclusions in the briefing document, which I think Dr. Wolfe alluded to in the open session, their comments that I think are similar to what Dr. Gerhard's saying that the extraction is relatively straightforward techniques. These aren't exotic solvents. These are ingestible solvents, and then common solvents under stress conditions accelerate the separation and so forth. So the fact that FDA is coming to those

conclusions, I'm having a hard time reconciling then with the proposed labeling.

But I do understand, though, the argument that Dr. Emala is saying. It's not all or nothing necessarily. It's somewhat of an arbitrary cut point. And it would have been helpful, given I'm sure there was a lot of careful thought on what the appropriate ratio was in the drug for its clinical development, to have had some discussion around how much is enough and so forth because we don't really have evidence.

Is it just a little bit that gets extracted, the naltrexone, that is sufficient, or do I have to hit a certain threshold? I'm sure that was well thought through in the clinical development in choosing the ratio that they had. So I feel a little uncomfortable reviewing all of these data, and having a presentation, and then having experts say, "Well, it's not all or nothing. Having something in there is good enough," which I respect them as experts in the field, but we really don't have evidence to look at in order to make a

judgment based on data.

Maybe others around the committee have familiarity as to the ratio of naltrexone to opioids that makes a clinical difference.

DR. BROWN: Dr. Winterstein?

DR. WINTERSTEIN: I would like to echo what was said. I think the issue is how much effort one would consider to have to be overcome in order to label something abuse deterrent. I think we all agree that there is probably nothing that is absolutely abuse deterrent. If we have a good chemist, they will always be able to do something with this, at least I trust chemists that they might.

I think what Dr. Gerhard was trying to relate to those of us who have memorized the solvents on this infamous slide MO-48, M21, 22, and 15 -- these are the ones that show these continuously brown bars down to the bottom.

These are those solvents that he described. You can go into a supermarket, buy them, throw the pills in there, and you will even enjoy what you

get out of it. That is a scenario that is different from I'm in my kitchen, and I have to come up with a small chemistry lab in order to extract something.

I think that needs to be weighed against the fact that if I'm just crushing them, which is probably what the majority of people who try to misuse those substances would try to do, if I just crush them, then there clearly is a positive effect of naloxone. We have seen that. How much that effect is really there in particular with higher doses, we're not completely sure about, either.

So I think the decision we need to make is do we go from simple crushing to trying to dissolve the substance and where would we start to set the bar for what is really abuse deterrent. And having had those discussions before, many of us have sat in meetings before that have looked at abuse-deterrent properties.

Oftentimes, it's about how do I get this extract out of a gel, right, or anything along these lines. So I think that's what we need to

weigh it against.

DR. BROWN: Dr. Gupta?

DR. GUPTA: Yes. I just want to comment on the conversation. I think that I agree with both of you that there is no perfect product that can be developed, but what was striking was that there were solvents that actually saw a fairly equal ratio of naltrexone and oxycodone. That's great.

We didn't see that across the board, though. There was just naltrexone that was low in some solvents, some that was very high. That's where I'm concerned. It doesn't matter how much was released, in my opinion. I think abusers will take what they can get. How long, it doesn't matter how long it takes.

If we saw there was a ratio of equivalence of naltrexone and oxycodone being distributed over a fair amount of point of time, that would be more convincing to me of preventing abuse. I don't know if it's something you can create, though.

DR. BROWN: Dr. Perrone?

DR. PERRONE: Jeanmarie Perrone. I just

want to start by saying that, in the FDA briefing document, they said in the safety evaluation, "ALO-02 administered in doses ranging from 10 milligrams up to 80 milligrams BID for up to 12 months has a safety and tolerability profile consistent with other opioids," which I will add, are not safe.

We've seen data that shows that these people are on these opioids with escalating doses over time. This is what we know happens. So all these abuse-deterrent formulations, to me, is a little bit of smoke and mirrors about whether or not we should approve another high-dose opioid with maybe some modest ADF effects.

I would agree that once you have a recipe and the recipe is similar to other recipes that are working on other abuse-deterrent formulations, once it's out there, it doesn't matter if there are 5,000 data points that didn't work. Once you get the one data point that does work, it will be the recipe that proliferates and is relatively simple given what we've looked at.

I'm just concerned about the whole issue, both the ADF properties and another high-dose opioid. This idea that the 80 milligrams maybe has the same likeability or even more likeability and we didn't see the data at the highest doses; that raises great concerns to me.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. Yes, I'd like to echo a lot of what's already been said, and one of the things to keep a focus on when we think about the real world is that it's not just abuse, but it's also diversion which creates the market for addiction. So when we talk about an addict only wanting five or 10 minutes and need my fix right now, yes, that's one player in the ecosystem of drug addiction and drug abuse.

When we have people who may be doctor shoppers and drug diverters with the intent to sell, what happens is -- when we look at street fentanyl, so when fentanyl gets out on the street, you have a significant increase in overdose deaths. What we're doing here now is offering the ability

to get a large amount of oxycodone that can be solubilized and then, if able to dry out, could be added to other street drugs. That could also increase the risk of overdose and death because now you're having much more potent stuff out there.

I think that's really important to realize. The second thing for me was that the same technology that was used in Embeda at least initially, as I understand it, did not get ADF labeling at that point.

I guess I think, overall, the big concern that I'm thinking about here is the ability with the solvents that are easily accessible and that the other half of this is the issue of diversion and the overdose deaths that could occur as a result of this stuff being diverted, dissolved, and then sold.

DR. HERTZ: I want to clarify. This is Dr. Hertz. I want to clarify that the lack of Embeda getting abuse-deterrent language upon its initial approval was not a result of the assumption that we didn't think the data were meaningful, as

implied. It represented a very early product evaluation, and we did not know at that time what to do with them.

As a result, we opted not to label, not because we decided it was good or bad. We decided broadly that we were not yet ready to label products with language relating to abuse-deterrent properties. As we started getting more data from more studies and more products, even different types of products, coming in, we started coming back to advisory committee, and we were discussing it more.

We developed an approach that led to our willingness to consider labeling under certain conditions. I could tell you more if you think you need to hear more, but the assumption that Embeda did not get labeling in 2008 is not a reflection of a decision that the data were problematic. It was a reflection of where we as an agency and the science of abuse-deterrent evaluation was at that time.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: I understand the context and the criteria with which FDA will ultimately make a decision, so I'm sharing this more as a little bit of a thinking process. This whole process of trying to arrive at abuse deterrence is sort of a moving target, and we've been learning as we went and trying to decide what's an acceptable increment of improvement and so on.

There's something unique about the product that we're looking at today, and that is that this technology is already on the market. So we have an opportunity, if you will, to make a better informed decision if only we wait for postmarketing data. That hasn't been an option in any of the other products that we've looked at because the technology had never been on the market before.

I'm just putting forward for consideration the concern that, since this is an evolving process, do we need that information before making a by-the-seat-of-our-pants shotgun decision on this being abuse deterrent? I don't have an answer on one side or the other of that question. It's just

something I haven't discussed so far.

DR. BROWN: If I could comment on that, we've been asking for postmarketing information on a number of different derivative products for a long period of time, and it doesn't appear that we're going to get that information about any products in the near term. So rather than saying that we're not going to come here and deal with any more products, I think that we're going to have to make a concerted effort to deal with what we have based on what we hear.

You are correct, though, in that the decision-making process of the advisory committee could be all wrong, and it could be all wrong because the decisions that have been made over time prior to the time that either you or I were on this committee were based on information that was true and unrelated and that postmarketing information will give us some correctability to that, but that is for the future. Unfortunately, nobody more than I wants that information.

Dr. Shoben?

DR. SHOBEN: Just a way in here, I do think that there's sort of an interesting issue as to where do you draw the line in terms of what is an unacceptable incremental improvement enough to get the abuse-deterrent labeling. For me at this point in time, I think they have met that standard very, very modestly.

I wouldn't expect any products to be worse, particularly with the oral administration just because of the potential for some level of experimentation and then a relatively easy extraction process to separate them.

But there is a significant time delay, and as Dr. Emala was talking about, there is some potential for some naltrexone to be released at the same time. And it is better to me that what is currently out there, at least in terms of deterring some level of oral abuse.

Similarly, like the discussion yesterday, if you do just crush it and take it, there is that deterrent to -- the easiest way to abuse it orally is a deterrent with this product.

Then I just wanted to add that I think that nasal and intravenous has been touched on, but I think there is significant evidence for the nasal and intravenous deterrent.

DR. BROWN: Can the members of the advisory committee speak to their differential thinking between the various routes of administration and then whether the oral route is more or less abuse-deterrent versus nasal and IV? Anyone make a comment on that?

Dr. Higgins?

DR. HIGGINS: I was persuaded more with the oral and nasal than I was with the intravenous, and that's largely because it was simulated assessment and that was hard for me to use that as a basis for Troxyca being safe for intravenous purposes. So I would vote more for the oral and nasal than I would intravenous.

DR. BROWN: Are there any other comments or discussion about this question number 1, please discuss whether there are sufficient data to support a finding that Troxyca ER oxycodone

hydrochloride and naltrexone hydrochloride extended-release capsules has properties that can be expected to deter abuse commenting on support for abuse-deterrent effects for each of the three possible routes of abuse: oral, nasal, and intravenous.

Dr. Emala?

DR. EMALA: I'll just throw a comment in to respond to your question. I think, if you're talking about the non-extracted formulation, if you're talking about a crushed formulation, I think the data is equally strong for all three categories.

I think if you're on the side of the fence that believes the extraction is an issue, then we don't know that data because it hasn't been studied as far as looking at extraction fraction for abuse potential. One would assume that it would not be good for any of the routes if you could successfully extract it.

But I think for the data presented in the non-extracted form, I think the data is strong for

deterrent in all three categories.

DR. BROWN: Any other? Dr. Shoben?

DR. SHOBEN: I would mostly agree. I would just say that the nasal -- in order to abuse nasally, you have to have the dried product so that, if you go for an extracted route, then you have to find a way to dry out the solvent. So in my mind, that is actually the strongest abuse deterrent here.

DR. BROWN: Dr. Winterstein?

DR. WINTERSTEIN: Yes. With respect to the intravenous part, I'm not getting the feeling that it's even the company's intent to have something that is abuse deterrent for IV use because IV use -- these are pellets, so IV use would mean that it has to be dissolved, and we talked about solvents. And there are solvents that could be used that would preferentially dissolve oxycodone.

So the whole idea with the pellets is for oral use, so I'm not completely sure why we would think that the intravenous --

DR. BROWN: Because of the release of

naltrexone.

DR. WINTERSTEIN: Yes, but somebody --

DR. BROWN: The pharmacokinetic --

DR. WINTERSTEIN: -- would need to manipulate the product at that point anyway. And that would involve a solvent, and then we're back to the solvent issue that we had before. That's why I'm --

DR. EMALA: Charles Emala. I was just responding to their IV simulated study suggesting that the co-administration would be protected, but I agree with you. It couldn't be without an extraction step.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. Just very quickly, so obviously, I'm worried about the oral route of abuse after extraction, but to differentiate, I'm not looking for a -- I understand the issue of abuse deterrence and that that's not a guarantee that it can't be abused. It's really an issue of effort, and I think I laid out why I think that for the oral routes, some of

the solvents might make that very straightforward.

For the other routes, obviously, after extraction if you could isolate oxycodone and then dry it, you can use any of these routes of abuse. But that extra work, I think that's then a deterrent. If you have to spend days of work to prepare a formulation for nasal or intravenous abuse, in a sense, that's fine.

But if it's just minimal effort, which I believe might be what is sufficient for oral abuse after straightforward extraction, that's just a different animal because it requires so much less work. It requires some time, but the actual work effort is fairly minimal.

DR. BROWN: Any other comments? If not, I'm going to try my best -- Dr. Campopiano?

DR. CAMPOPIANO: Just one really quick comment, it's not that I disagree with anything that's been said, but I just want to put in the real world of opioid misuse right now, which is if you have even a somewhat burdensome process to get a pharmaceutical pure product, if you compare that

from the drug user's perspective to the possibility of using heroin with some unknown amount of acetyl fentanyl that will kill you before you have a chance to even say help, I think that we need to be careful about not being too reductionistic about the fiendish drug user who's only going to wait for a couple of minutes before they need gratification.

The decision-making and risk benefit is a little bit different in today's world in regards to opioids for misuse because of the acetyl fentanyl that is so widely available --

DR. BROWN: I think that your comments are important, and I want to understand a little bit better. I didn't really understand where you were going with that with those comments.

DR. CAMPOPIANO: I was trying to be quick. I'm sorry.

DR. BROWN: Don't worry about it.

DR. CAMPOPIANO: So there's illicitly manufactured fentanyl that is a white powder, and it's very widely present in parts of the country as either a phony pill or a contaminant to different

degrees in white powder heroin. The user who obtains these substances doesn't know that there could be fentanyl in there or how much, and fentanyl, as you know, is very quick acting and rapidly fatal.

Even if there's someone present -- typically, an overdose take a few hours. You're under-ventilated for a period of time, so there's a chance that somebody will stumble upon you, and if that person happens to be able to call 9-1-1 or administer naloxone, you might live. But this stuff is the kind of the needle-in-arm overdose scenario, and it's causing a larger and larger portion of overdoses among people who misuse opioids.

So from the point of view of the drug user, if this is what your alternative product is, the idea of putting this pharmaceutical that you know is manufactured by a reputable company through a simple dissolution and then a drying process, even if it takes some time, is probably not the kind of barrier that it once was when heroin was more

expensive and not very pure. Now it's cheap, and pure, and likely to kill you because it's got some unknown amount of fentanyl in it.

There are even manufactured phony pills that look like branded or generic versions of known pharmaceuticals that actually don't contain that pharmaceutical but contain illicitly manufactured fentanyl.

I know the conversation has been a little bit simplistic around the idea that a sufficient deterrent is something that delays gratification for a few minutes or requires a little bit of effort. I think that's kind of simplistic to start with. If drug users were that primitive, they wouldn't probably survive in their substance abuse for very long.

Then the world of substances that are available on the street are much more deadly, and so people are seeking ways to meet their own needs and sustain themselves that are less likely to kill them. So I don't know if I made it worse or I made it more clear.

MS. CHAUHAN: Cynthia Chauhan. Am I correct in what I'm hearing you say is we should not underestimate the determination of the abuser?

DR. CAMPOPIANO: Yes, very simply and eloquently put. Thank you.

DR. BROWN: Any other comments?

(No response.)

DR. BROWN: To summarize, I think the committee is in a quandary about Troxyca ER. It appears on one hand to fulfill criteria for abuse deterrence by all three routes of abuse. On the other hand, it also appears to be capable of being manipulated in such a fashion that it relatively effortlessly can be changed into a drug of abuse.

The data that have been presented today, in my mind, are not clear in that regard. Having said that, I think that the sponsor has been eloquent in their presentation in trying to give us all the information that is currently available, but it's not apparent from what I can hear from the community that we as a community have an understanding of whether the abuse deterrence in

this drug is going to be robust.

A couple of other comments, the medication does offer the ability to be used by patients that have difficulty swallowing which is one thing that I always think of.

There are questions about the issue of the 80-milligram formulation for this drug and whether in general we should be putting high dose formulations of long-acting opioids on the street, not particular to this drug but really for all the long-acting drugs that we see.

Lastly, there's still a question, in my mind, as to whether the formulation of 80 milligrams begins to act like an immediate-release formulation in terms of whether or not the taker would use it again at a higher dose rate. I think the postmarketing information would help us with these things. Unfortunately, we don't have those.

Anybody have any other comments to add to my choice of summary?

(No response.)

DR. BROWN: If not, we're going to take a

15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 3:20.

(Whereupon, at 3:06 p.m., a recess was taken.)

DR. BROWN: So we're going to move to question 2, "Should Troxyca ER be approved for the proposed indication of management of pain severe enough to require daily around-the-clock long-term opioid treatment and for which alternative treatment options are inadequate?"

Questions or comments prior to taking a vote on this? We've had some discussion prior to this. Hearing none --

DR. HERRING: Dr. Brown?

DR. BROWN: Yes.

DR. HERRING: If I could just make one comment, I'm new to this committee, but from the perspective of the reviews that we've had last month and this month on abuse-deterrent

formulations, I would encourage the committee to consider not only the totality of the data the sponsor's presented beyond just the solutions and dissolution profiles, but also the clinical data and also to encourage consistency in the committee with what we consider to be a reasonable degree of incremental benefit, which we've discussed previously, and keep that in mind in this case.

I think it is in our collective interest to continue to figure out how we can make modifications to these medications to help patients and to serve the broader needs of the community. And I think in this situation, some of the conversation has to be kind of focus in on what I think is a relative minority group in abusers that would go to fairly extreme efforts in order to manipulate a drug.

I'm just encouraging that we keep that in mind in terms of context as we go forward talking about this particular product. Thank you.

DR. BROWN: We will be using an electronic voting system for this meeting. Once we begin to

vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all the questions have been answered or discussed.

Once again, question 2, "Should Troxyca ER be approved for the proposed indication of management of pain severe enough to require daily around-the-clock long-term opioid treatment and for which alternative treatment options are inadequate?"

If there are no questions or comments concerning the wording of the question and no further discussion, please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly.

After you have made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote is 9 yes, 6 no, zero abstain.

DR. BROWN: Now that the vote is complete, we're going to go around the table and everyone who voted, state their name, vote and if you want to, you can state the reason why you voted as you did into the record.

I'm going to start with Dr. Gupta.

DR. GUPTA: Dr. Anita Gupta, I voted no. I really appreciate the work that was done by the FDA

and the sponsor. I really recognize that there's been significant progress that's been done, but I have several concerns on the product that was presented.

One, the imbalance of the ratio of release of oxycodone, naltrexone with several simple solvents, as we discussed, needs to be clarified in detail. The amounts of drug released, the time span of those release, the potential for further manipulation after release needs to be clarified.

Second, there was a lack of clarify on how much added value the product adds to prevent abuse deterrence. And three, there was really a lack of clarity on what happens with drug-liking at higher dosages as compared to the control.

Although I understand a lot of the points that were made about delivering a drug to provide analgesia, the information presented today really lacks a lot of clarity for me, and I think those points need to be clarified.

I really encourage all of you, FDA and sponsors, really to find those answers. There's

potential promise in the product you've presented, potentially innovative solutions that can be created that could be novel really to provide safe use of opioids.

DR. BESCO: Kelly Besco, I voted yes. In terms of it being an effective extended-release product, not necessarily commenting on abuse deterrence quite yet. I felt the evidence today showed that it is as effective as current products that are on the market. That's why I voted yes.

DR. WINTERSTEIN: Almut Winterstein, I voted yes for similar reasons. I did not consider the issue of abuse deterrence in my vote. I just considered the issue of efficacy and usual risk in my vote, and that's why I voted yes.

DR. MORRATO: Elaine Morrato and I voted yes. Also took a more narrow interpretation in terms of whether or not the data presented met regulatory standards for approval, not issues on the incremental market value and so forth. And my issue was more on whether or not to grant the abuse-deterrent claim or not, which we'll discuss

in the next votes.

DR. SHOBEN: Abby Shoben, I voted yes. I think it does meet the current standard for approval for an ER opioid. Whether or not that standard is appropriate is a different issue, but I think it has met the current standard.

DR. BROWN: Rae Brown, I voted yes.

MS. CHAUHAN: Cynthia Chauhan, I voted no. My reasons are in line with Dr. Gupta's.

DR. KAYE: Alan Kaye, I voted yes for the reasons mentioned. I think it meets the standards as of today.

DR. EMALA: Charles Emala, I voted yes from the context of its effectiveness as an analgesic.

DR. McCANN: Mary Ellen McCann, I voted yes. It appears to be efficacious as an analgesic.

DR. CAMPOPIANO: Melinda Campopiano, I voted no because it is demonstrated to be as safe and effective as our standard, but the evidence would seem to point to this class of drugs not being particularly safe nor being particularly effective for chronic pain in general. So I wasn't

comfortable voting yes for this product.

DR. SPRINTZ: I'm Michael Sprintz. I voted no. When I interpreted the statement where it says should it be approved for the proposed indication, in terms of pain management, it said, "And for which alternative treatment options are inadequate."

Well, I think that we have plenty of long-acting oxycodone preparations already that are out there, some with abuse-deterrent properties and some without, but in terms of just straight pain management, I think there's a lot of alternatives that are already on the market.

DR. PERRONE: Jeanmarie Perrone, I voted no. I don't support another high-dose opioid on the market unless it meant that it replaced other non-abuse-deterrent formulations. The new guidelines that we have from the CDC recommend against using opioids for chronic pain, especially in the long run.

If we don't start acknowledging other guidelines that post-date the research that was

done for this drug, then each drug gets approved based on the fact that another drug already got approved. So at some point, we have to stop and change what our criterion are.

DR. HIGGINS: Jennifer Higgins, I voted yes. I was convinced by the efficacy and safety data.

DR. GERHARD: Tobias Gerhard, Rutgers. I agree the product meets the current standard. It's no less safe or less effective than the other extended-release opioids. Nonetheless, I voted no because I agree with some of the previous commenters that the current standard is what brought us the opioid epidemic that we're dealing with, so we have to start making some changes at some point.

DR. BROWN: If we can go to question 3, "If approved, should Troxyca ER be labeled as an abuse-deterrent product by the oral route of abuse?"

Are there any questions or comments concerning the wording of the question? If not, we'll open the floor for discussion or further clarifying questions. And if there are none, we

will now begin the voting process.

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly after you've made your selection. The light may continue to flash.

If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote was 6 yes, 9 no, zero abstain.

DR. BROWN: Now that the vote is complete, we're going to go around the table and have everyone who voted state their name, their vote. And if you want to, you can state the reason why you voted as you did.

This time we're going to start with Dr. Gerhard.

DR. GERHARD: Tobias Gerhard. I voted no. While I recognize the efforts of the sponsor and I don't want to let the perfect be the enemy of the

good when we want to make progress with abuse-deterrent formulations, I am worried that there is the possibility to achieve significant extraction and separation of the naltrexone, extraction of the oxycodone and separation from the naltrexone with common, readily available, and ingestible solvents.

It takes some time, but it's, I think, so easy to do that I'm worried. I haven't seen enough data to convince me otherwise, and we in a sense have to start trying to raise the standards when it comes to granting this status. As we've heard in some of the public comments, if the perception is that these drugs may be perceived by prescribers as more safe, less likely to lead to addiction, all things that have not been shown with any data, then we have to be very careful with granting that status.

Again, I think I said this yesterday, it doesn't require abuse of these drugs to become addicted to these drugs. So if granting that abuse-deterrence status creates that impression, we create an even bigger problem.

DR. HIGGINS: I'm Jennifer Higgins. I voted yes. To my mind, abuse deterrent does not mean abuse proof. I also think the benefits outweigh the risk, and I support additional options for consumers.

DR. PERRONE: Jeanmarie Perrone. I voted no as per Dr. Gerhard.

DR. SPRINTZ: Michael Sprintz. I voted no also for the reason as Dr. Gerhard.

DR. McCANN: Mary Ellen McCann. I voted yes. I think the time is a significant deterrent, so I would consider it a deterrent.

DR. CAMPOPIANO: Melinda Campopiano. I voted no.

DR. EMALA: Charles Emala. I voted yes. I thought this had two layers. One was the non-extracted crushed product, which I thought the data presented was quite strong in favor of a deterrent.

When I considered the extraction discussion, I think we could all agree, it depends on where you want to draw the line. But even in the worst case scenario, if there's substantial time involved, we

could argue that in and of itself has a degree of deterrence. So for those reasons, I voted yes.

DR. KAYE: Alan Kaye, I voted yes. I believe as a clinician, naltrexone even at a very, very low dose even in the most extreme extraction version, the data is compelling enough to vote yes.

MS. CHAUHAN: Cynthia Chauhan, I voted no for reasons already stated.

DR. BROWN: Rae Brown, I voted yes.

DR. SHOBEN: Abby Shoben, I voted yes largely for the reasons stated by Dr. Emala and Dr. Kaye. I just wanted to reiterate this idea that I think it's much stronger for the crushing route of abuse than for the potential sort of extraction. And barring additional data, I would hope that the label claims would be making more modest statements about the extraction possibility.

DR. MORRATO: Elaine Morrato, I voted no. I was on the fence on this. I found it a very difficult question. I recognize the reason why we convene committees like this is we don't have standards. And as I sat on several of these panels

trying to be internally consistent with myself, it's challenging because it's a moving target even over the last couple of months. Each company is learning from the prior on how to present data, and each company has a unique package of data.

So it's somewhat hard to be comparing apples to oranges sometimes. And I recognize this makes it difficult for sponsors as well as the FDA on how you chart the course and what level of evidence is sufficient, consistency of evidence across the different categories of studies, how much deterrence is enough, how much effort is needed to overcome deterrence.

I ultimately voted no. Partly, I agree that the non-extracted crushed manipulation, the studies that were shown there did demonstrate abuse deterrence across the Category 1 and Category 3 studies in terms of oral and the liking. But I felt that the level of difficulty in overcoming was enough for me to give pause and why I voted no.

What would be the evidence I would have liked to have seen or discussed that we didn't have

time for today? I understand that some naltrexone is better than no naltrexone. It's not an all or nothing.

I would have liked to have seen some data -- and perhaps the company has this data and they can follow up with FDA with it -- trying to better understand what's the minimum amount of extraction that's necessary to have a clinical benefit. How do you best interpret the brown boxes?

You might even say I really wish they had done a Category 3 study in which they had crushed with some sort of form of extraction, not just the physical manipulation, but something to do with the chemical as well.

Ideally, this is the drug that's been on the market longest. Maybe it didn't have the abuse-deterrence claim, but it's certainly had the abuse-deterrent formula. And it would have been nice to have had some post-market evidence. I appreciated the survey data that was presented in follow-up by one of the sponsor's experts, and I wish we had had

more discussion around that sort of post-market environment and how this kind of mechanism is really being used other than some anecdotal information on a website.

But I just want to lastly say that this is, I think, exactly why it's important to have advisory committees, to debate these issues because, otherwise, the data that was presented today isn't in the public domain, and all the public sees is what's in a label, and it's a sentence or two. And I recognize that you can't have everything in the label, but this allows at least this debate to be in public record and for individuals and associations to be considering the full breadth of information. Thank you.

DR. WINTERSTEIN: Almut Winterstein. I voted no mainly for the same reasons that Dr. Gerhard stated. But I would also like to point out that this is a guess from all of us, how far people will go, and that actually is the main reason I voted no. Because what that means is we make a label decision based on a guess. Whether it's in

one direction or the other, we basically don't know.

I think that that shows us that we really need to raise the bar for the types of studies that are required to make labeling decisions like that. Theoretically, I think ideally, as this determination of abuse deterrence would really be made postmarketing and not upon approval, because we really don't know what people will do with those medications.

So in general, perhaps that really should not be a discussion that should happen in the approval phase at all unless there really is the magic bullet that shows up that we would all agree that there is no way to abuse this particular medication. But in general, I think that the requirements to show that something really is abuse deterrent, those standards should be reevaluated, and they should be raised.

DR. BESCO: Kelly Besco. I voted no for reasons that have been stated about the data and the manipulation of the intact product.

DR. GUPTA: Dr. Anita Gupta, I voted no for the reasons already mentioned and what we heard from Dr. Gerhard.

I really believe that as a member of this committee, it is our responsibility to really redefine what the abuse-deterrence standards are. I know there is guidance for industry, but given the climate we're in, we have a lot of ownership on making sure we define that standard, and that we raise the bar, and that we're clear on what that is.

I know there's a lot of discussion and we're trying to figure that out as we go, but I don't believe as we currently are represented with a product that it truly showed that potential for promise for abuse deterrence. There needs to be more information that's provided so we can understand that better.

DR. BROWN: We're going to move on to question 4. Question 4 is, "If approved, should Troxyca ER be labeled as an abuse-deterrent product by the nasal route of abuse?"

Are there any questions or comments concerning the wording of this question? If there are not, then we'll move on to ask about clarifying questions or discussion, further discussion. And if there is not any further discussion, can we please move on to a vote?

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash.

If you're unsure of your vote or you want to change your vote, please press the corresponding button until the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote is 11 yes, 4 no, zero abstain.

DR. BROWN: Now that the vote is complete, we're going to go around the table again and have everyone who voted state their name, their vote and if you want to, you can state the reason.

We're going to start with Dr. Gupta down

there.

DR. GUPTA: Dr. Gupta. I voted no for the reasons already mentioned.

DR. BESCO: Kelly Besco. I did vote yes for this one. I felt that there was sufficient data that showed that when the product was crushed, it did not separate.

DR. WINTERSTEIN: Almut Winterstein, I voted no because I tried to be a consistent person. I agree that simple crushing of the product will likely result in less liking than in a product that would not contain naltrexone. It comes back to the discussion about effort, so essentially what would make this still open to abuse would be if the substance were first dissolved, and then dried, and then nasally used.

Obviously, this is a little bit more complicated, so I understand why some of my committee colleagues voted yes, but again, this is a guess of how far people would go in order to manipulate a product because we really don't know the data for this.

That's the main reason I voted no. I really think that we need to have different standards for the evaluation of abuse deterrence upon approval in order to make that determination.

DR. MORRATO: Elaine Morrato, and I voted yes. I agree with Dr. Winterstein that in terms of standards and that discussion and what's really appropriate at time of approval, I would agree.

I was applying the current standards that we have. So why did I switch on this one? I still have the same concerns around the extraction. I still recognize that the abuse-deterrent Category 3 studies did show crushing was a deterrent. So I was sort of swung over by Dr. Shoben's comment earlier that the extra step of extraction and drying would be another layer, and barrier, and a deterrent.

Being on the fence for this one, I swung over the fence and said yes on abuse-deterrent claim. But we still need more postmarketing.

DR. SHOBEN: Abby Shoben. I voted yes for reasons that I stated during the discussion, and it

was really significant separation between the crushed, this product and the immediate-release form in the Category 3 studies. It was really quite compelling.

DR. BROWN: Rae Brown, and I voted yes.

MS. CHAUHAN: Cynthia Chauhan, I voted yes. I thought the data was better for the nasal than for oral.

DR. KAYE: Alan Kaye. I voted yes for the reasons already mentioned.

DR. EMALA: Charles Emala, I voted yes.

DR. McCANN: Mary Ellen McCann, I voted yes.

DR. CAMPOPIANO: Melinda Campopiano, I voted no, and it has to do with -- I guess I fall in the other side of the line of how much of a barrier the manipulation of the product represents.

I also, much as I know FDA and the sponsor are working in the environment of the now, just couldn't bring myself to green-light it without postmarketing data. I feel like that's even more important to give it this positive endorsement on partial evidence.

DR. SPRINTZ: I'm Michael Spritz, and I voted no. I do agree that when taken in the narrow context of just crushing without extraction, that that has deterrent properties. However, I think with the extraction, I think that that actually has a significant thing.

The other thing I wanted to mention to is the idea of unintended consequences of labeling abuse deterrent and the importance that we need to educate prescribers on actually understanding abuse as well as diversion and addiction in both the nature of those things and the differences between them, but also how to identify abuse, diversion, and addiction and what to do if a prescriber runs into that.

I think part of that should be involved when we talk about abuse deterrence. It also involves education as well.

DR. PERRONE: Jeanmarie Perrone. I voted yes.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. GERHARD: Tobias Gerhard, I voted yes, and also switched from the previous vote for the same reasons Dr. Morrato did, I think, here. The extra effort is enough to warrant a deterrence claim.

However, I'm echoing Dr. Sprintz. I think it's critically important that if the drug is approved and abuse-deterrent labeling for any route is granted, that some language is included in the same section that makes it clear that abuse-deterrent formulation does not protect from addiction. I think that's just something that's critically important, not just for this product but generally for opioids that want an abuse-deterrent claim on the labeling.

DR. BROWN: Let's move on to question number 5, our last question. "If approved, should Troxyca ER be labeled as an abuse-deterrent product by the intravenous route of abuse?"

Are there any questions or comments concerning the wording of this question? If not, are there any questions or comments about

clarifications relating to our previous discussions? If there are none, let's move on to our vote. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote.

(Vote taken.)

DR. BEGANSKY: The vote is 9 yes, 6 no, zero abstain.

DR. BROWN: We're going to go around the table, and I think it's Dr. Gerhard's turn to start.

DR. GERHARD: Tobias Gerhard. I voted yes for all the reasons I stated in the previous question.

DR. HIGGINS: Jennifer Higgins. I voted no for the reasons I mentioned earlier.

DR. PERRONE: Jeanmarie Perrone. I voted yes, and I would like to say that perhaps we can move towards -- if we can get more abuse-deterrent formulations on and all the other ones off the market, that would be great.

DR. SPRINTZ: Michael Sprintz, and I voted

no for all the reasons I've stated previously.

DR. CAMPOPIANO: Melinda Campopiano. I voted no for reasons stated previously.

DR. McCANN: Mary Ellen McCann. I voted yes.

DR. EMALA: Charles Emala. I voted yes.

DR. KAYE: Alan Kaye. I voted yes.

MS. CHAUHAN: Cynthia Chauhan. I voted no.

DR. BROWN: Rae Brown, I voted yes, and since this is the last vote, I'm going to take the opportunity to make a few comments.

The current requirements for the FDA place the agency in a situation where there's not much room not to approve drugs such as this no matter what we want. However, what we've heard over the last two days -- and I think it's beginning to be quite repetitive -- is we're beginning to hear a drum beat for limiting the number of ER/LA drugs on the market.

I think it's important that with the larger federal juggernaut of actions that are going on, that some consideration be given to consideration

of that at some higher level.

I've heard continuous entreaties to develop some standards to promulgate to sponsors for how much is enough abuse deterrent and how can that be maintained in any drug, and I think that's very important.

The third thing I would say is that some of these abuse-deterrent drugs have been on the market for quite a long time now. And as I said before, I really fear that this committee and perhaps the agency are making decisions about drugs such as this in a vacuum of no data. And I worry constantly about our inability to do the right thing, which I think we all want to do, without being able to see postmarketing data.

So once again, I'm going to ask that the agency make some concerted effort to get those data out so that we can begin to evaluate them so that we can know if the decisions that we're making are the right decisions.

DR. SHOBEN: Abby Shoben, I voted yes.

DR. MORRATO: Elaine Morrato, and I voted

yes for the reasons stated for my vote for the nasal route. I'm going to add an additional comment as well. I think it's important also for consistency that in light of today's discussion that the Embeda labeling should also be reviewed. Unless there's data to the contrary, the underlying mechanism of deterrence is the same, and I think it's very important that the statements around the deterrent properties be consistent.

We also discussed briefly earlier about that statement of around how you imply the degree of dissolution and all of that could be vague and could be over-interpreted as opposed to conservatively interpreted.

I think there would be value in looking back at that. Softening the language, I guess, is how Dr. Emala had mentioned it and that that be consistently applied across both of the drugs unless there's data to contradict that.

Then another piece here is, again, we're trying to ensure consistency across these various committees. There's going to be future ones as

well. I just really, as I mentioned yesterday, encourage the FDA as we develop future briefing documents that the rolling history of the decisions that are being made get continued and updated.

We already had in our briefing document today a drug that was reviewed a couple of months ago, and so understanding how the FDA came to decisions when the advisory committee voted one way or another is helpful in helping us all standardize. Not all of us are going to be on all committees at all time, and I think it's part of the learning process to make sure that we are consistent in how we're applying our thinking in terms of building out the standards ourselves.

DR. WINTERSTEIN: Almut Winterstein. I voted no for the reasons already stated.

DR. BESCO: Kelly Besco. I voted yes for reasons I stated with the last vote.

DR. GUPTA: Dr. Anita Gupta. I voted no for the reasons previously stated.

DR. BROWN: If there are no more comments, before we adjourn, are there any last comments from

the FDA?

DR. HERTZ: Just one more thank you to all of you. It's really been interesting to be working on these products over the years and to hear the evolution of the comments from the committee members. And we'll take all of this conversation back for further discussion within the agency and see if we can evolve some of our thinking.

Adjournment

DR. BROWN: If everybody on the advisory committee will just remember to pick all of your belongings with you, the room is cleaned at the end of the day. All materials left on the table will be disposed of. Please remember to drop off your name badge at the registration table so that it may be recycled.

I'd like to just add my thanks to all of you. You've been great over the last two days, and thank you.

(Whereupon, at 3:55 p.m., the open session was adjourned.)